Universidade de Aveiro Departamento de Química
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Cycloaddition Reactions of *Meso*-tetraarylporphyrins

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Dissertação apresentada à Universidade de Aveiro para cumprimento dos requisitos necessários à obtenção do grau de Doutor em Química, realizada sob a orientação científica do Professor Doutor José A. S. Cavaleiro, Professor Catedrático do Departamento de Química da Universidade de Aveiro

"Fundação para a Ciência e a Tecnologia" (FCT), Portugal (BD/2936/2000)

o júri

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palavras-chave

Porfirinas e compostos análogos. Clorinas. Reacções de ciclo-adição; transformações de Diels-Alder, 1,3-dipolares e electrocíclicas.

resumo

O trabalho apresentado nesta dissertação descreve o comportamento de *meso*-tetra-arilporfirinas em reacções de ciclo-adição e suas possíveis aplicações na síntese de novas porfirinas com grupos policíclicos aromáticos ("π-extended porphyrins").

No capítulo 1 apresenta-se uma revisão das aplicações de porfirinas e compostos afins e também das reacções de ciclo-adição que envolvem ligações duplas (periféricas) do macrociclo.

O capítulo 2 descreve o trabalho feito em reacções de cicloadição 1,3-dipolar de *meso*-tetra-arilporfirinas com iletos de azometino.

Considerou-se primeiramente a reactividade de *meso*-tetra-arilporfirinas simétricas perante iletos de azometino. Em seguida estudaram-se as reacções de *meso*-tetra-arilporfirinas de tipo A_3B também com iletos de azometino. Seguidamente consideraram-se estudos similares mas desta vez visando reacções de cicloadição 1,3-dipolar, intramolecular, com *meso*-(o-formilfenil)porfirinas.

O capítulo 3 descreve os estudos efectuados sobre transformações de Diels-Alder de *meso*-tetra-arilporfirinas com *orto*-quinodimetano de tipo pirazínico. Os novos produtos ("π-extended porphyrins") obtiveram-se por ciclização intramolecular entre grupos *meso*-arilo e o anel quinoxalínico fundido em β.

No capítulo 4 descrevem-se os estudos de ciclo-adição 1,3-dipolar de iletos N-piridínicos contendo o macrociclo porfirínico. As reacções de tais iletos com quinonas e com acetilenodicarboxilato de dimetilo originaram porfirinas subsituidas em posição *meso* com grupos de tipo indolizina. Essas quinonas foram usadas em excesso, actuando como dipolarófilos iniciais e depois como oxidantes. Obtiveram-se novos compostos aromáticos policíclicos nas reacções daqueles iletos com alcenos electronicamente deficientes e na ausência de oxidante.

O capítulo 5 relata os resultados dos estudos de síntese de porfirinas com grupos policíclicos aromáticos através de reacções electrocíclicas. Isso foi conseguido a partir das reacções de porfirinas contendo grupos cetónicos com iletos de fósforo. A caracterização estrutural destes novos derivados fez-se recorrendo ao uso de técnicas espectroscópicas modernas, especialmente através de estudos de RMN. Estes métodos de RMN incluíram métodos mono e bidimensionais (1D: ^{1}H, ^{13}C, DEPT; 2D: COSY, NOESY, HSQC, HMBC).

keywords

Porphyrins and analogues, chlorins, cycloaddition reactions, Diels-Alder reactions, 1,3-dipolar cycloadditions, electrocyclic reactions.

abstract

The work presented in this dissertation describes the cycloaddition reaction studies concerning *meso*-tetraarylporphyrins and also their applications in the synthesis of novel π-extended porphyrins.

Chapter 1 is a review on the applications of porphyrin derivatives and also on the cycloaddition reactions involving the peripheral double bonds of porphyrins.

Chapter 2 is related with the 1,3-dipolar cycloaddition reactions of *meso*-tetraarylporphyrins with azomethine ylides. Firstly, the reactivities of symmetrical *meso*-tetraarylporphyrins in the reactions with azomethine ylides were investigated; secondly, the 1,3-dipolar cycloaddition reactions of A_3B type *meso*-tetraarylporphyrins with azomethine ylides were also carried out; thirdly, the intramolecular 1,3-dipolar cycloaddition reactions of *meso*-(o-formylphenyl)porphyrins were also studied.

Chapter 3 is related with Diels-Alder reactions of *meso*-tetraarylporphyrins with pyrazine *ortho*-quinodimethane. The novel π-extended porphyrins were obtained from the intramolecular ring closure reactions between the *meso*-aryl group and the β-fused quinoxaline ring.

Chapter 4 is related with 1,3-dipolar cycloaddition reactions of porphyrinic pyridinium *N*-ylides. The reactions of porphyrinic pyridinium *N*-ylides with quinones and dimethyl acetylenedicarboxylate afford *meso*-substituted indolizine porphyrins. The quinones were used in excess, acting as dipolarophiles and as oxidants. The novel polycyclic aromatic compounds were obtained from the reactions of porphyrinic pyridinium *N*-ylides with the electron-deficient alkenes in the absence of any oxidant.

Chapter 5 is related with the synthesis of polycyclic aromatic porphyrin analogues via electrocyclic reactions.These novel analogues were synthesized from the reactions of ketone-bridged porphyrins with phosphorus ylides.

For the structural characterizations of the new compounds modern analytical techniques were used, with a special emphasis on NMR spectroscopic studies. These NMR methods include 1D: ^{1}H, ^{13}C, DEPT; 2D: COSY, NOESY, HSQC, HMBC.

Contents

Chapter 3: Diels-Alder reactions of *meso*-tetraarylporphyrins with pyrazine *ortho*-quinodimethane

Chapter 4: 1,3-Dipolar cycloaddition reactions of porphyrinic pyridinium *N*-ylides

Chapter 5: Synthesis of polycyclic aromatic porphyrin analogues *via* electrocyclic reactions

Abbreviations

AMD – age related macular degeneration

Ar – aryl

Bu – butyl

CID – collision-induced decomposition

CNT – carbon nanotube

COSY – correlated spectroscopy

d – doublet

DBU – 1,8-diazabicyclo-[5,4,0]undec-7-ene

dd – double doublet

δ – chemical shift

DEPT – distortionless enhancement by polarization transfer

DMAD – dimethyl acetylenedicarboxylate

DDQ – 2,3-dichloro-5,6-dicyano-1,4-benzoquinone

dt – double triplet

EI – electron impact ionization

ESI – electrospray ionization

Et – ethyl

FAB – fast atom bombardment

FDA – Food and Drug Administration

HBC – hexa-*peri*-hexabenzocoronene

Hex – hexyl

HMBC – heteronuclear multiple-quantum coherence

HOMO – highest occupied molecular orbital

HpD – hematoporphyrin derivatives

HSQC – heteronuclear single-quantum coherence

Hz – Hertz

ISC – inter-system crossing pathway

J – coupling constant

LDA – lithium diisopropylamide

LUMO – lowest unoccupied molecular orbital

m- – meta-

m – multiplet

Me – methyl

Mes – mesityl

MPcS – sulfonated metallophthalocyanines

MS – mass spectrum

m/z – mass-to-charge ratio

NBA – 3-nitrobenzyl alcohol

NEC – Nippon Electric Corporation

NIR – near-infrared

NLO – nonlinear optical

NMR – nuclear magnetic resonance

NOESY – nuclear Overhauser effect spectroscopy

o- – ortho-

OLED – organic light-emitting diode

*o*QDM – *o*-quinodimethane

p- – para-

PAH – polycyclic aromatic hydrocarbon

PDT – photodynamic therapy

PET – photoinduced electron transfer

Ph – phenyl

ppm – parts per million

Py – pyridyl

q – quartet

R_f – retention factor

s – singlet

t – triplet

TCNE – tetracyanoethylene

TDCPP – *meso*-tetrakis(2,6-dichorophenyl)porphyrin

TEA – triethylamine

TFA – trifluoroacetic acid

TfO – triflate

THF – tetrahydrofuran

TLC – thin-layer chromatography

TMS – tetramethylsilane

TOF – time of flight

TPFPP – *meso*-tetrakis(pentafluorophenyl)porphyrin

TPCD – tetrapyridinecobalt(II) dichromate

TPP – *meso*-tetraphenylporphyrin

UV-Vis – ultraviolet-visible

Publications

Reaction of *meso*-tetraarylporphyrins with pyrazine *ortho*-quinodimethanes
Shengxian Zhao, Maria G. P. M. S. Neves, Augusto C. Tomé, Artur M. S. Silva, José A. S. Cavaleiro, Maria R. M. Domingues, and A. J. Ferrer Correia
Tetrahedron Lett. **2005**, *46*, 2189-2191.

Novel porphyrin-quinone architectures *via* 1,3-dipolar cycloaddition reactions
Shengxian Zhao, Maria G. P. M. S. Neves, Augusto C. Tomé, Artur M. S. Silva and José A. S. Cavaleiro
Tetrahedron Lett. **2005**, *46*, 5487-5490.

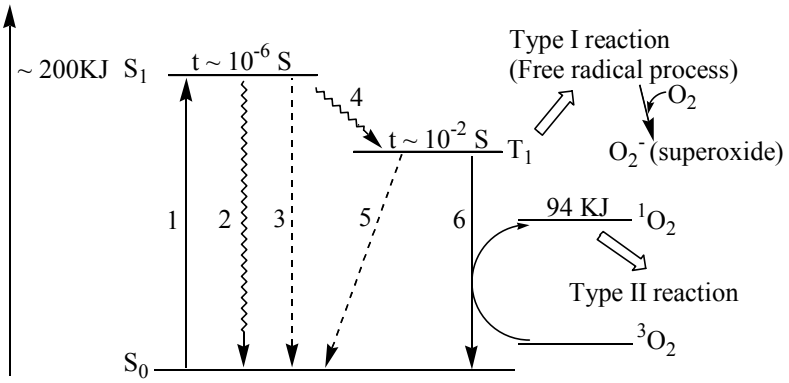
Chapter 1: Introduction

Porphyrins constitute an important class of macrocycles with some well known biological representatives such as hemes, chlorophyll and vitamin B_{12}. The word *porphyrin* is derived from the Greek *porphura* meaning purple, since all porphyrins are intensely colored. The UV-Vis spectrum of a typical porphyrin consists of a strong short-wavelength B band (Soret band) and weak long-wavelength Q bands. The porphyrin derivatives play a number of critical biological roles in the nature. Recently porphyrin functionalizations have become the current focus of research mainly due to their applications in diverse fields such as supramolecular chemistry,[1] materials,[2] biomimetic models for photosynthesis,[3] catalysis[4] and medicinal applications.[5]

1.1: Applications of porphyrin derivatives

Photodynamic therapy is a medical treatment which employs the combination of light, oxygen and a drug. After accumulation of a photosensitizer in malignant tissue, the illumination with light of an appropriate wavelength creates a photochemical reaction producing singlet oxygen (Type II reaction), which is the key agent of cellular damage, to destroy or modify some unwanted tissue. In other words, the Type II reaction predominates over the Type I (superoxide O_2^- might be generated). This process is described in the modified Jablonski diagram (Figure 1.1). A good photosensitizer can undergo the 'forbidden' inter-system crossing pathway (ISC, route 4) with very high efficiency. Another important photophysical property is the singlet oxygen quantum yield, the efficiency of transferring the energy of the absorbed light from the triplet state of the photosensitizer to triplet oxygen and thereby generating singlet oxygen (route 6). PDT treatment has a long history, the ancient Egyptians used the combination of some plants containing light-activated psoralens and sunlight to treat vitiligo over 4000 years ago. In 1995, Photofrin®, a purified version of hematoporphyrin derivatives (HpD) initially

developed by Roswell Park Cancer Institute (Buffalo, NY), became the first porphyrin-type PDT agent approved by the US Food and Drug Administration (FDA). It has also won regulatory approval in Canada, Japan and throughout Europe.[6]



1. Absorption; 2. Nonradiative Decay; 3. Fluorescence;
4. Intersystem Crossing; 5. Phosphorescence; 6. Energy Transfer

Figure 1.1: Modified Jablonski diagram

However, Photofrin® has demonstrated important disadvantages. Its accumulation in skin may last up to six weeks causing skin photosensitivity, especially under strong sunlight.[7] Also, because it is a complex mixture of porphyrins with oligomeric forms, no pure and active compounds has yet been isolated and characterized. Thus, no adequate interpretation of dose-response relationship can be made.[8] Its long wavelength absorption falls at 630 nm, which lies well below the wavelength necessary for the maximum tissue penetration. These considerations have led, since early 1980's, to the search for new and improved porphyrin derivatives, namely, 2nd and 3rd generation PDT drugs such as, for instance, Temoporfin and the chlorophyll derivatives NPe6 and HPPH.[9] It should be noted that cancer treatment no longer exclusively drives the development of these drugs. For example, age related macular degeneration (AMD), the major cause of blindness in elderly has no existing adequate therapy, but recently PDT has been successfully applied to control the symptoms of AMD.[10] One of the second generation photosensitizers, Verteporfin (BPD-MA) is recommended as a PDT-type photosensitizer for the treatment of the 'wet form' of AMD.[9] Presently, photodynamic therapy (PDT) constitutes one of the more promising new modalities being explored for use in a variety of medical applications.

An ideal PDT drug should fulfill certain requirements as follows:

Strong absorption in the red part of the visible spectrum (> 650 nm)

High quantum yield of triplet formation, with a triplet energy greater than 94 $kJmol^{-1}$

High singlet oxygen quantum yield

Low dark toxicity

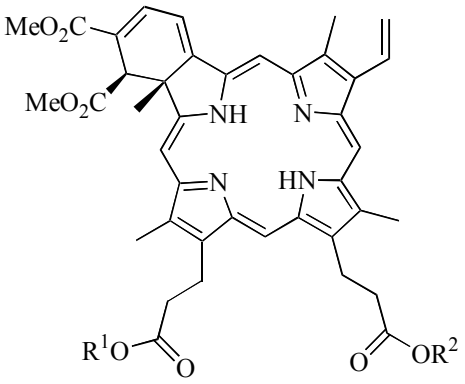
Must exhibit selectivity for the enrichment in tumorous tissue *vs.* healthy tissue, particularly skin; general skin sensitization must be avoided

Simple formulation of the drug; formulated drug should have a long shelf life

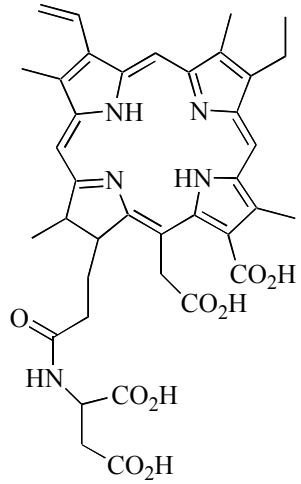
The pharmacokinetic profile should be that it rapidly clears from the body

Option for facile (side chain) derivatization to allow for improvement of the above properties

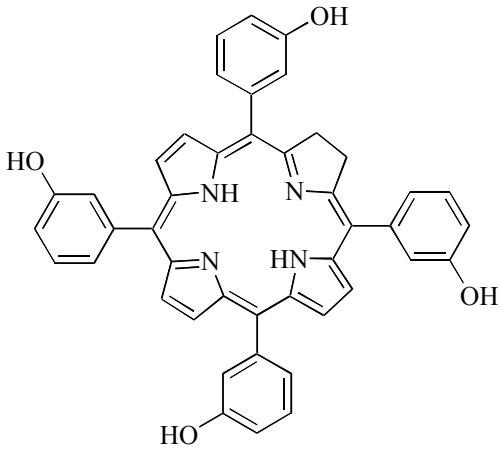
Facile synthesis from readily available starting materials, easily translated into kilogram scale



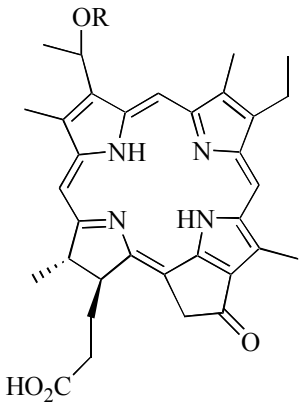
BPD-MA (Verteporfin)
Mixture of two isomers
R^1 = Me; R^2 = H
R^1 = H; R^2 =Me



NPe6



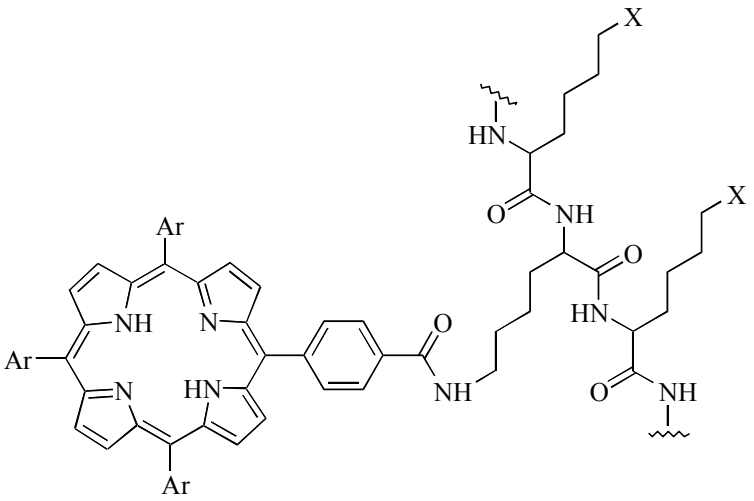
Temoporfin



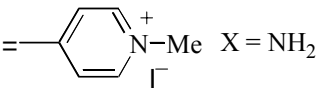
HPPH, R = 1-hexyl

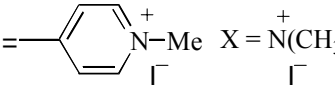
Some second generation clinical photosensitizers

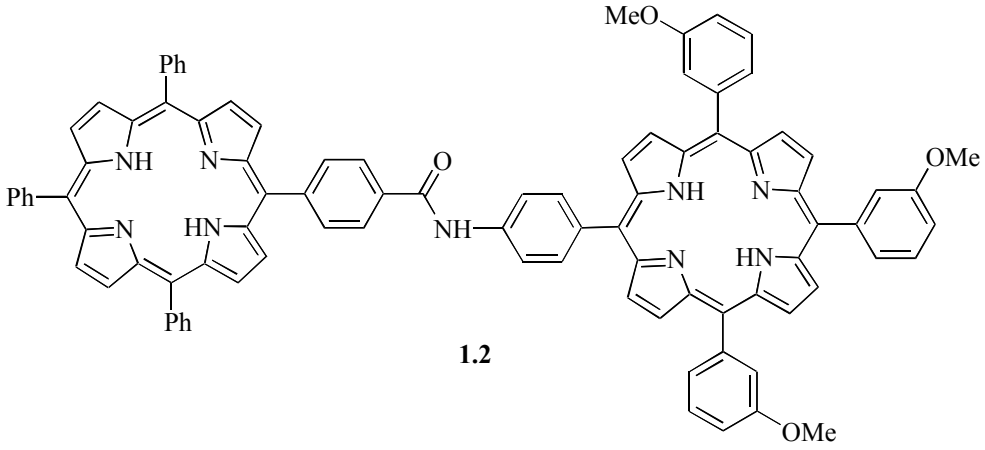
Recently, a wide variety of porphyrin derivatives have been investigated as photosensitizers in PDT towards developing a new drug. In order to investigate the effect of the position of hydroxyl groups on biological activity, Bonnett synthesized a series of *o*-, *m*-, *p*-isomers of *meso*-tetrakis(hydroxyphenyl)porphyrins to investigate the effect of the position of hydroxyl groups on biological activity of PDT treatment.[8] Among these isomeric porphyrins, the *ortho*- isomer was found to be highly phototoxic. However, the *meta*- and *para*- isomers showed promising activity and tissue selectivity in photonecrosis. Especially, the *meta*- isomer was found to be about 25 to 30 times more potent than HpD.[11] For an ideal photosensitizer, solubility in water is a major requirement. Cationic porphyrins[12] and porphyrins conjugated with hydrophilic biomolecules such as sugars,[13] nucleosides,[14] peptides[15] have been synthesized and investigated as photosensitizers. The Aveiro group has synthesized new conjugates of poly-*S*-lysine with cationic porphyrins **1.1**. The new conjugates **1.1** were used in the photoinactivation of antibiotic-resistant Gram-positive bacteria and Gram-negative bacteria.[16] Since Photofrin® consists a mixture of porphyrin oligomers, our group has also investigated the pharmacokinetic behavior and photodynamic properties of porphyrin dimers like **1.2**.[17]



1.1

a, Ar =  X = NH_2

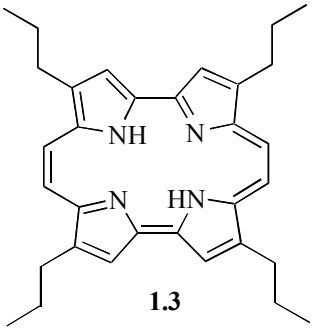
b, Ar =  X = $N(CH_3)_3$



1.2

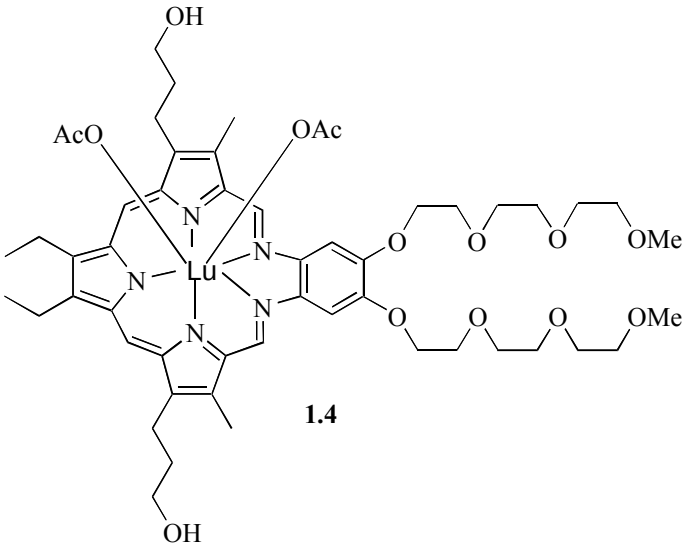
An ideal sensitizer should absorb light around 750-800 nm, not only because of its deeper tissue penetration, but also due to the availability of cheaper diode lasers for sensitizer excitation. Chlorins show photophysical properties similar to those of the porphyrin systems,[18] but have enhanced Q bands (~ 650 nm) which make chlorin-containing systems better candidates for PDT. The same applies to bacteriochlorins with absorption bands at $\lambda > 700$ nm. The optical spectra of bacteriochlorins lies within the ideal region for PDT. However, due to their unstable nature, synthesis of stable bacteriochlorins has been a challenge for porphyrin chemists. Bonnett *et al.* have investigated the PDT efficacy of *meso*-tetrakis(hydroxyphenyl)chlorins isomers.[19] Among these analogues, the *meta*- isomer appeared to be the most promising candidate for PDT.[20] Bonnett *et al.* also synthesized *meso*-tetrakis(*m*-hydroxyphenyl)bacteriochlorin.[19] Biological test showed that it was a very active tumor photosensitizer, but, it was relatively unstable, about 25 to 33% of this bacteriochlorin within cells was oxidized to chlorin in 24 hours.[21]

Vogel *et al.* synthesized porphycenes, the isomeric porphyrins, from diformylbipyrrole.[22] The parent unsubstituted porphycene is a very nonpolar compound with a porphyrin-like spectrum (λ_{max} 630 nm). Guardiano *et al.* found that porphycene **1.3** was selectively transported by serum lipoproteins and was delivered to tumor tissue with good efficiency and selectivity (tumor vs normal tissue: 16.7:1).[23] Another type of porphyrin isomer, the '*N*-confused' porphyrin, was independently isolated and characterized by the groups of Furuta[24] and Latos-Grażyński.[25] The '*N*-confused' porphyrins exhibit long-wavelength absorption near 700 nm, which makes them suitable candidates for use in PDT.



1.3

In recent years, numerous expanded porphyrins have been discovered and studied.[26] The expanded porphyrins provide potential photosensitizers for PDT. Sessler *et al.* reported a new class of expanded porphyrin, the so-called texaphyrins, prepared by a Schiff base condensation.[27] The texaphyrins absorb strongly in the 720-780 nm spectral region. The metallotexaphyrins are particularly useful in PDT due to the high-yield production of long-lived triplet states and their remarkable efficiency as singlet-oxygen-producing photosensitizers. Among all the metallotexaphyrins tested for PDT so far, lutetium(Ш) texaphyrin appears to be the most promising one.[28] Lutetium texaphyrin **1.4** is a water-soluble drug with strong absorption at 732 nm. In a mouse tumor model, lutetium texaphyrin **1.4** had significant efficacy in treating neoplasms of moderates size (40±14 mm^3) and in treating larger neoplasms.



1.4

Compared to porphyrins, phthalocyanines offer high molar-extinction coefficients (~ 10^5) and red-shifted absorption maximums at 680 nm, which make them potential

photosensitizers. Phthalocyanines are excellent singlet oxygen generators. Interestingly, chelation of a metal ion such as zinc and aluminum increases the singlet-oxygen efficiency to nearly 100%.[29] The PDT efficacy of water-soluble sulfonated metallophthalocyanines (MPcS) has been studied in details both *in vitro* and *in vivo*. Brasseur *et al.* showed that the mono- and disulphonated derivatives of Ga-, Al-, and Zn(PcS) are most active, whereas the tri- and tetra-sulphonated dyes are less efficient sensitizers.[30]

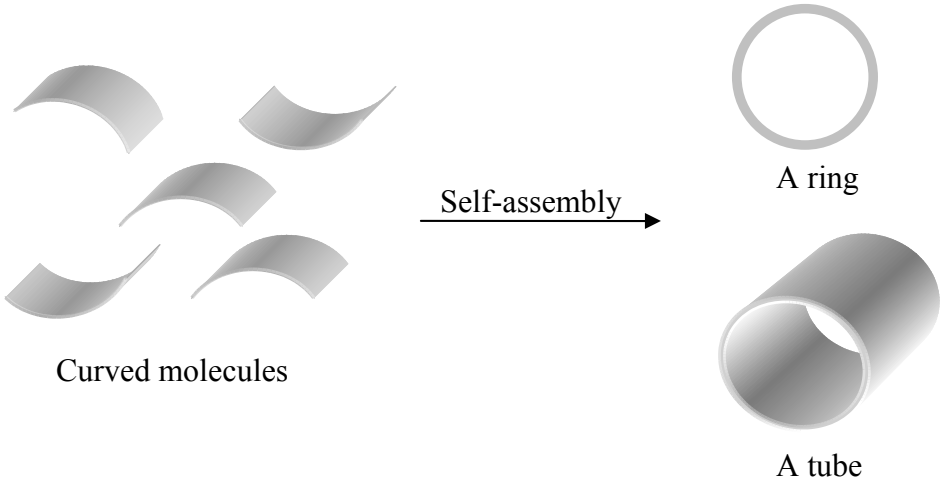
Recently, porphyrins became attractive components for building supramolecular systems since they are potential electro- and photoactive moieties.[31] Porphyrins have been investigated as receptor models for recognizing alcohols,[32] quinones,[33] fullerenes,[34] sugars,[35] amino acids,[36] peptides,[37] DNA,[38] and RNA.[39] The recognition of the cationic acceptor viologen derivatives has also been investigated because of the structural analogy to the photosynthetic pigments.[40] Calixpyrroles[41] and expanded porphyrins[26] are novel anion receptors. Porphyrins are poor anion receptors, since these systems can not rely on direct pyrrole NH-anion interactions; however if the porphyrin macrocycle contains an adequate substituent, such binding type interaction can be performed *via* that substituent.[42] Combinations of porphyrin and other hosts such as crown ethers,[43] cryptands,[44] calixarenes,[45] and cyclodextrins[46] have also been reported. Chiral porphyrins have been designed and synthesized as the model receptors for chiral recognition and asymmetric catalysis.[4,47]

Novel supramolecular architectures such as interlocked molecules (catenanes and rotaxanes),[48] dendrimers,[49] helicates[50] incorporating porphyrins as fundamental components have been synthesized for catalysis,[51] photoinduced electron transfer,[52] molecule imprinting,[53] nanosensors,[54] organic nanotubes.[55]

Interaction of chiral molecules with other molecules (chiral or achiral molecules) at the supramolecular level can lead to the transfer of chiral information, that is, chirality induction in the achiral component or chirality amplification of the total system. This phenomenon was named as supramolecular chirogenesis. Ethane bridged bis(Zn porphyrin) was used as achiral host molecules for studying this phenomenon.[56]

The study of objects which are anywhere from hundreds to tens of nanometers in size has recently been referred to as nanoscience. It is a growing field of research in chemistry,

physics, and biology. Nanotubes have attracted considerable attention since the discovery of carbon nanotubes (CNT) by Iijima (NEC) in 1991.[57] Since the highly substituted porphyrins are distorted, a tube structure can be constructed by self-assembly of molecules with a curved surface (Scheme 1.1), and in this way Kojima et al. prepared a porphyrin nanotube inclusion of tetranuclear molybdenum-oxo clusters.[58] The development of uniform nanometer sized particles has been intensively pursued because of their technological and fundamental scientific importance.[59] Some porphyrin nanoparticles have been prepared and revealed high catalytic activities.[60]

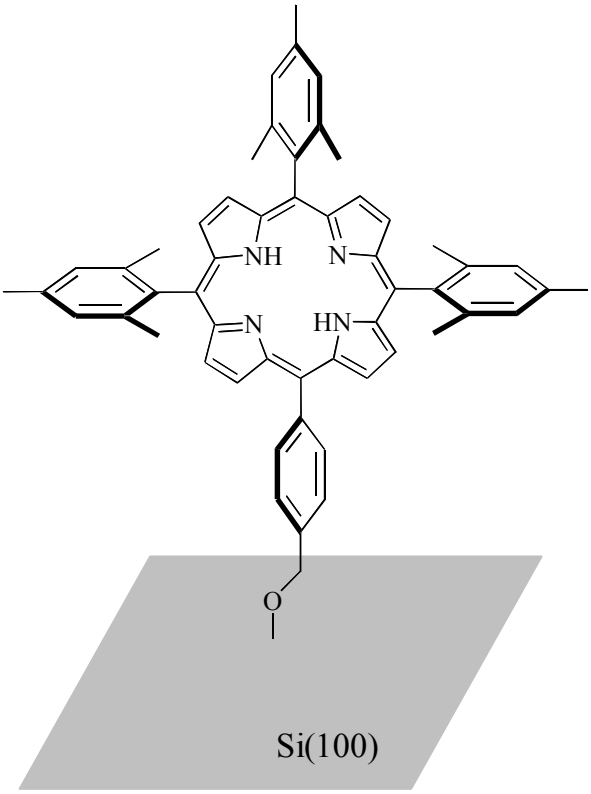


Scheme 1.1: Conceptual description of the self-assembly of curved molecules

Today, the computational devices become more and more powerful. This development is accomplished with the miniaturization of the silicon chip, the top-down approach. Decades ago, Intel co-founder Gordon Moore predicted that the devices per chip would be doubled every 18-24 months, and this so-called "Moore law" has been proved true over past years. However, this top-down approach will reach its physical limit in the near future. An alternative is the bottom-up approach, where molecules possessing some inherent function have been synthesized, then assembled with other components to build the electronic device. It was first suggested by Aviram and Ratner in 1974.[61] Today, molecule-scale electronics still is a young and active field.

Lindsey *et al.* suggested that data may be stored in the oxidation states of molecule, especially, porphyrin derivatives. Since porphyrins provide three accessible oxidation

states: the neutral state, monocation, and dication, porphyrins form stable radical cations and dications and undergo reversible electrochemistry. They investigated different porphyrin derivatives for multibit information storage.[62]



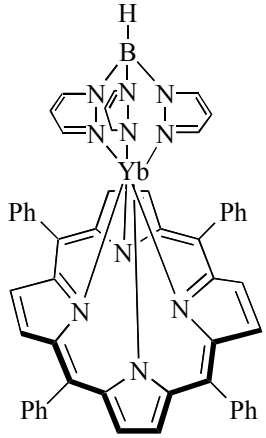
Si-tethered porphyrin for the information storage study

The highest occupied and lowest unoccupied molecular orbitals (HOMO and LUMO) of porphyrins are separated by around 2 eV. If this gap is little narrowed then molecules will have useful electrical properties required for molecular wires. The redox properties of such systems can be controlled by the modifications and metal chelations of porphyrins. Another advantage to the use of porphyrins as molecular wires is the large size of the monomeric unit. Two types of conjugated porphyrin oligomers can be used as the potential molecular wires; one type is to bridge the multiporphyrin arrays *via* other π systems such as aromatic systems[63] or simple alkyne[64] molecules and another type involves directly 'fusing' porphyrins together.[65]

Nonlinear optical (NLO) materials have extensive applications in areas such as optical limiting, information storage, optical switching.[66] It is known that organic molecules with

push-pull structure show large second-order NLO properties and materials with long conjugated π-systems exhibit strong third-order nonlinearities.[66a,67] Porphyrins are potential candidates for such NLO materials due to the large π-conjugated system and versatile modifications of the structures. Indeed, porphyrins have been shown to have good second-order[68] and third-order[69] nonlinearities.

Organic chromophores with strong absorptions and/or emissions at NIR region can be used as potential sources for telecommunication, defense, and medicinal applications.[70] NIR electroluminescence devices based on porphyrins have been reported.[71]



NIR luminescent Yb porphyrin complex

Solar energy conversion is one of the most attractive topics for the twenty first century, because it has potential to solve energy and environmental problems. Meanwhile, photosynthesis is one of the most complicated processes in Nature. It is essential for living organisms to convert solar energy into chemical energy, the core of photosynthesis is the photoinduced multistep electron transfer between donors and acceptors in the reaction center. A large number of biomimetic model systems have been constructed for the photoinduced electron transfer discussion. Porphyrin derivatives with large π-electron systems are particularly well suited for this task, firstly because their molar extinction coefficients are high, and secondly, because they absorb light over a wide spectral range. Therefore, porphyrin-based light-harvesting complexes[72] and donor-acceptor linked molecules[73] have been prepared to understand photoinduced electron transfer and photosynthesis.

1.2: Cycloaddition reactions involving the peripheral double bonds of porphyrins

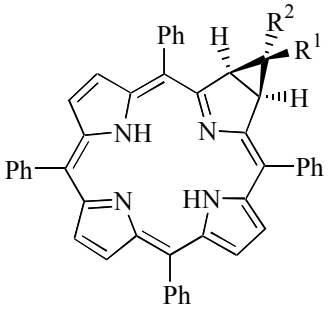
Porphyrin chemistry has undergone a renaissance over the past ten years due to the extensive applications of these compounds. The chemical functionalization of porphyrins with different types of substituents at the β- and *meso*-positions has become an active and exciting field in organic chemistry.

It is well known that partial isolation of double bonds at the porphyrin periphery shows many parallels with the chemistry of simple alkenes and explains the peripheral addition, reduction, oxidation and pericyclic reactions.

Over the past years, we and other people have shown that peripheral double bond(s) of the porphyrin macrocycle can participate in different cycloadditions.[74]

1.2.1: [2+1] Cheletropic reactions

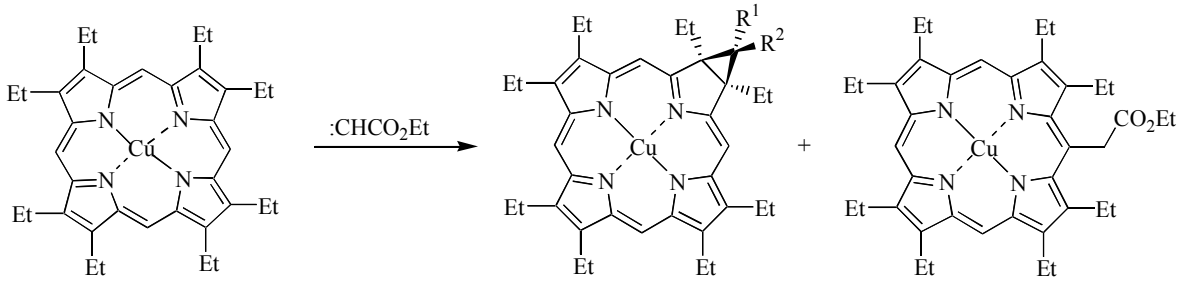
Cyclopropanation reactions have been widely used in organic synthesis. Addition of carbenes generated from diazomethane, methyl diazoacetate, and dimethyl diazomalonate in the presence of CuCl, to *meso*-tetraphenylporphyrin (Zn complex) gave, after demetalation, chlorins **1.5** in 20-30% yields.[75] With methyl diazoacetate the bacteriochlorin was also formed.



1.5

a, $R^1 = R^2 = H$
b, $R^1 = CO_2Me$, $R^2 = H$
c, $R^1 = H$, $R^2 = CO_2Me$
d, $R^1 = R^2 = CO_2Me$

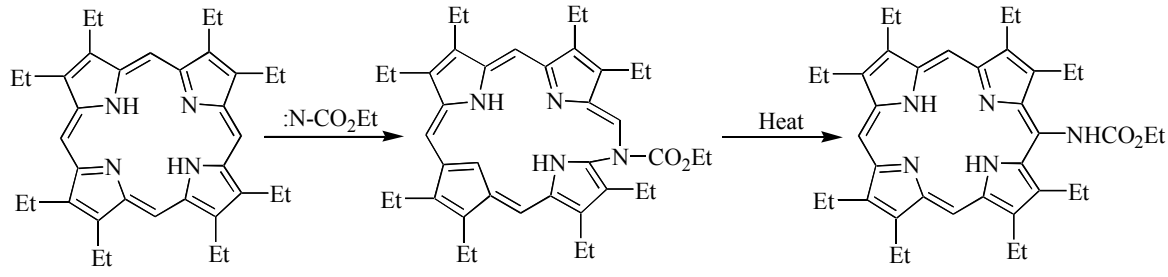
The *meso*- unsubstituted porphyrin **1.6** reacts with ethyl diazoacetate in the presence of copper(I) iodide to produce two isomeric cyclopropanechlorins **1.7a,b** as main products, and *meso*-ethoxycarbonylethylporphyrin **1.8**, by addition of the carbene respectively to a peripheral double bond and to a *meso* position (Scheme 1.2).[76]



1.6 **1.7a,** $R^1 = H$, $R^2 = CO_2Et$; **1.7b,** $R^1 = CO_2Et$, $R^2 = H$ **1.8**

Scheme 1.2

Aziridinations of porphyrins have also been investigated, but no aziridination products were obtained.[77] Octaalkylporphyrins such as octaethylporphyrin **1.9** react with ethoxycarbonylnitrene (generated *in situ* from ethoxycarbonylazide or ethyl-*N*-*p*-nitrophenylsulphonyloxycarbamate) to give ring-expanded *meso*-homoazaporphyrins such as **1.10**, resulting from attack at a *meso*-double bond. These compounds undergo ring contraction, upon heating or in the presence of copper or zinc acetate, to afford *meso*-ethoxycarbonylaminoporphyrins such as **1.11** (Scheme 1.3). The reaction of the Cu or Zn complexes of octaethylporphyrin with ethoxycarbonylnitrene gave the corresponding metal complex of **1.11** directly.

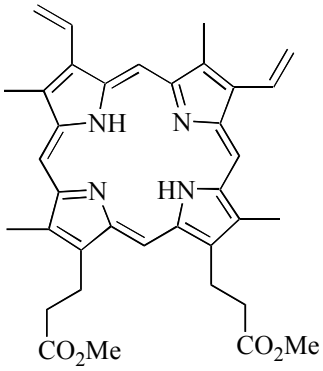


1.9 **1.10** **1.11**

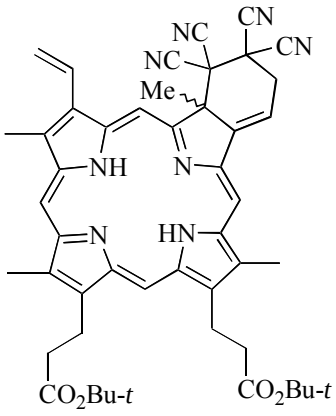
Scheme 1.3

1.2.2: [4+2] Cycloaddition reactions

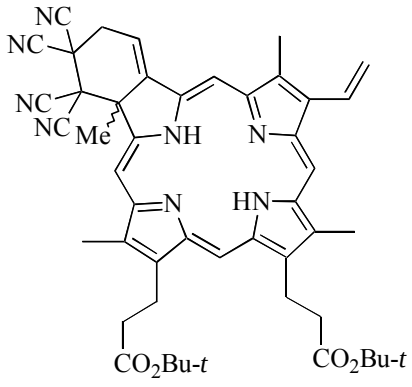
Thirty years ago, the reactivity of protoporphyrin-IX dimethyl ester **1.12** with tetracyanoethylene (TCNE) and dimethyl acetylenedicarboxylate (DMAD) was reported to afford isobacteriochlorins (bis-adducts).[78] Subsequent reinvestigation of the reaction of protoporphyrin-IX di(*t*-butyl) ester with TCNE have shown more complicated results.[79] Mono-adducts **1.13-1.15** and bis-adducts **1.16-1.19** from [2+2] and [4+2] cycloadditions were obtained, the expected isobacteriochlorin **1.19** was only isolated in minor amounts.



1.12



1.13



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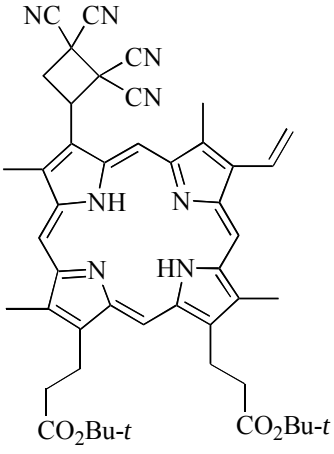
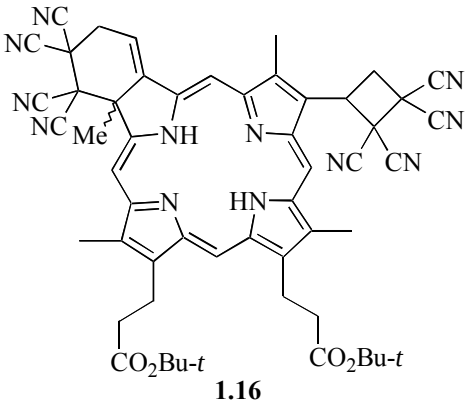


1.15



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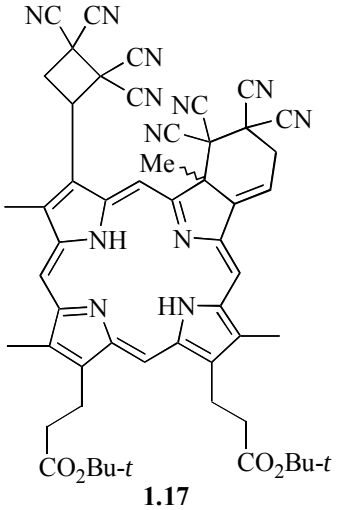
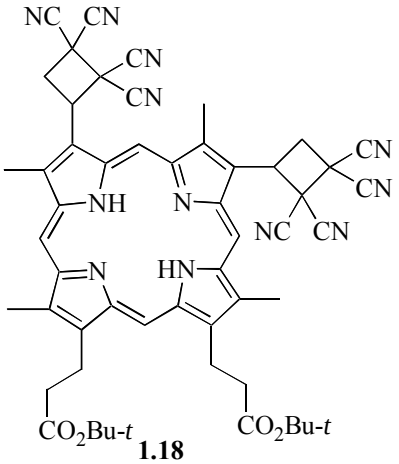


1.17



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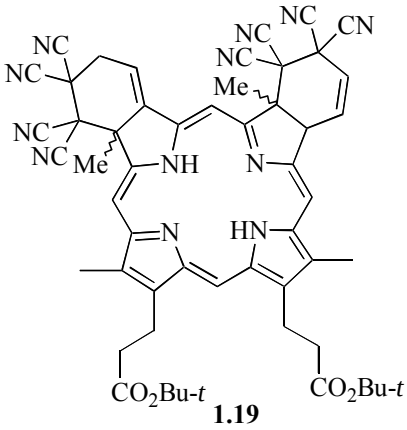
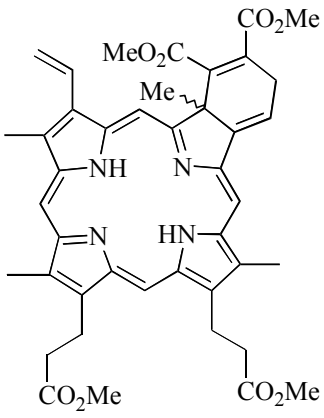
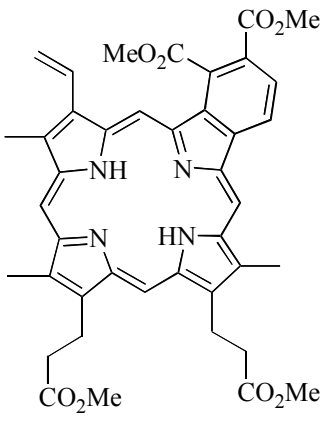


1.19

The reaction of protoporphyrin-IX with DMAD was also revised. Only monoadducts were obtained (*e.g.* **1.20**), the elimination of the angular methyl group was described to afford monobenzoporphyrins **1.21**.[80]

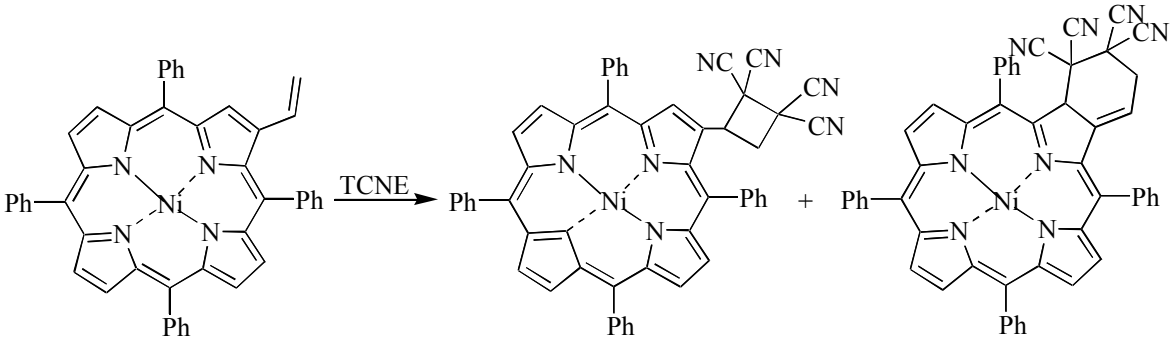


1.20



1.21

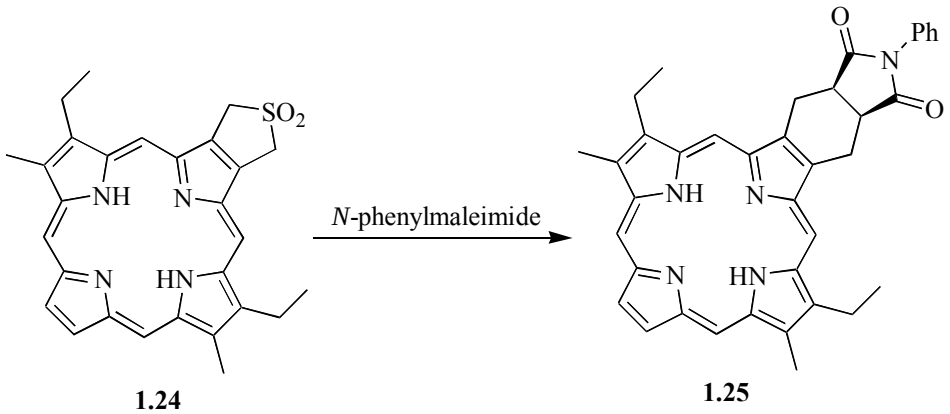
The possibility of β-vinyl-*meso*-tetraarylporphyrins to act as dienes in Diels-Alder reaction was also investigated.[81] It was found that reaction of 2-vinylTPP (Ni complex) with an excess of tetracyanoethylene (TCNE) afforded adducts **1.22** and **1.23** (Scheme 1.4), NMR studies showed that the [2+2] adduct **1.22** can be obtained by the rearrangement of the [4+2] chlorin **1.23**.



1.22 **1.23**

Scheme 1.4

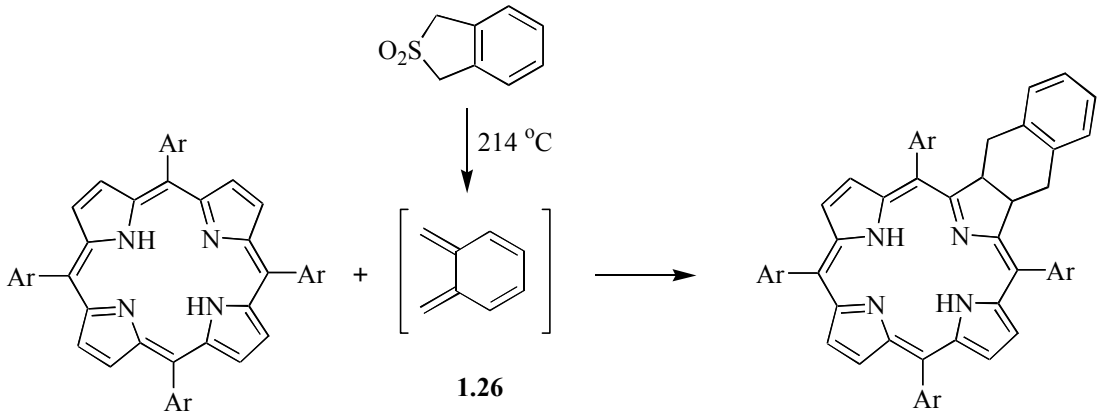
Aromatic fused 3-sulfolenes have been widely used as precursors for highly reactive *ortho*-quinodimethanes, and normally a high temperature is necessary for the extrusion of sulfur dioxide. However, on heating porphyrin-fused 3-sulfolene **1.24** in toluene at moderate temperatures (80-110 ^{o}C) in the presence of dienophiles such as *N*-phenylmaleimide, the corresponding Diels-Alder adduct **1.25** was isolated (Scheme 1.5).[82]



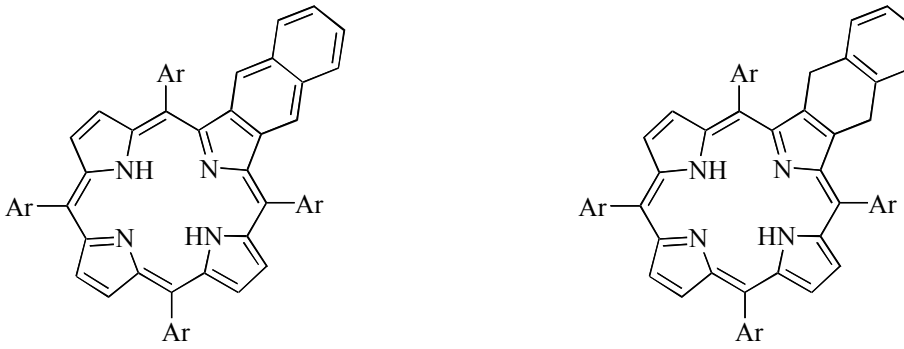
1.24 **1.25**

Scheme 1.5

It was shown by our group that the peripheral double bonds of the porphyrins can participate in Diels-Alder reactions, as the 2π electrons component.[83] TPP reacted with *ortho*-benzoquinodimethane **1.26** (QDM) generated *in situ* by the thermal extrusion of SO_2 from 1,3-dihydrobenzo[*c*]thiophene-2,2-dioxide to give chlorin **1.27a** (Scheme 1.6), together with two oxidized compounds **1.28a** and **1.29a**.

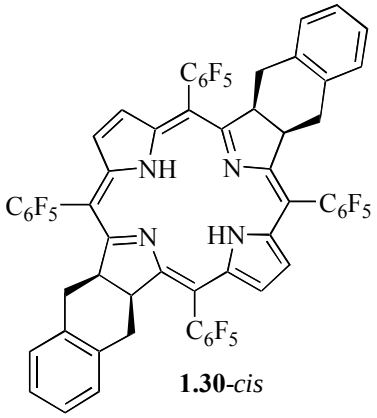


Scheme 1.6

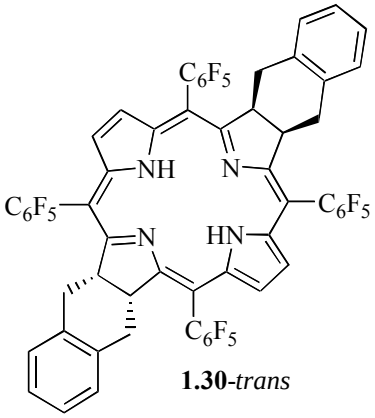


However, when *meso*-tetrakis(pentafluorophenyl)porphyrin (TPFPP) was used as dienophile, **1.28b** and **1.29b** were not formed. Together with chlorin **1.27b**, two stereoisomeric bacteriochlorins **1.30** (*cis* and *trans*) were obtained. The formation of bis-adducts can be explained by the fact that TPFPP is more electron-deficient than TPP and electron-deficient alkenes are more reactive in Diels-Alder reactions. Since electron-

deficient compounds are more difficult to oxidize, it is not surprising that chlorin **1.27b** does not dehydrogenate to porphyrins **1.28b** and **1.29b**.

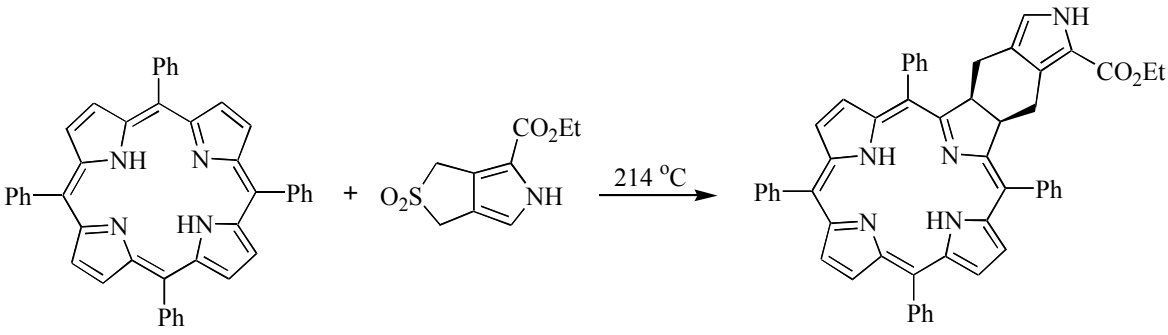


1.30-*cis*



1.30-*trans*

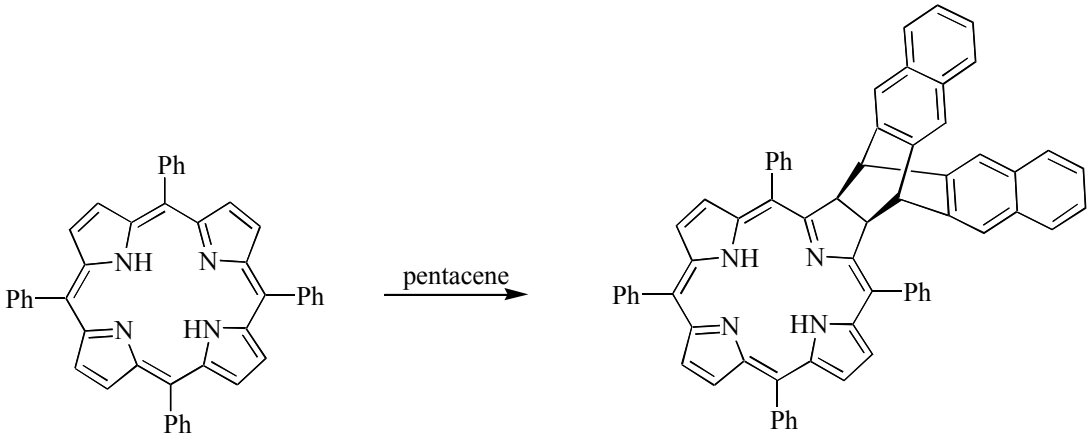
Smith *et al.* also reported a Diels-Alder reaction of *meso*-tetraarylporphyrins with pyrrole *o*-quinodimethane.[84] The isoindole-fused chlorin **1.31** was obtained from the [4+2] cycloaddition reaction of TPP with pyrrole QDM in refluxing 1,2,4-trichlorobenzene (Scheme 1.7).



1.31

Scheme 1.7

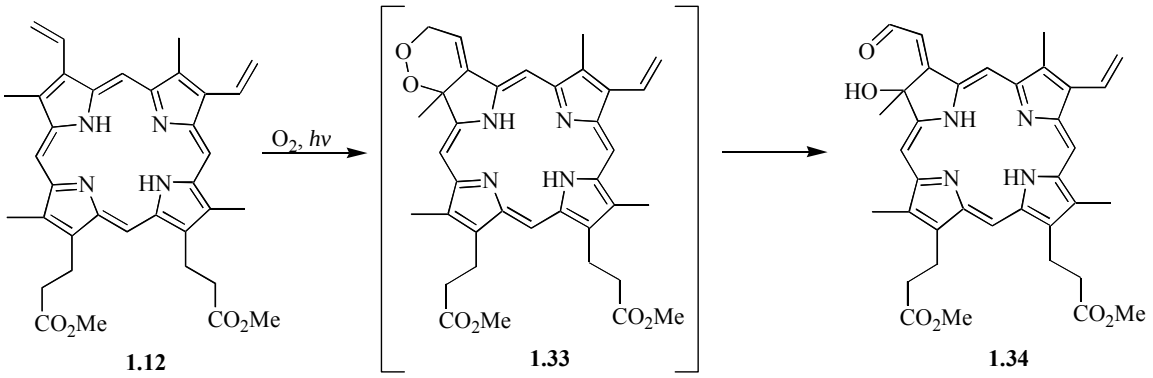
Our group has also shown that porphyrins react with ‘‘stable’’ dienes like the commercially available polycyclic hydrocarbon pentacene.[85] When a mixture of this compound and TPP in 1,2,4-trichlorobenzene is heated at *ca* 200 °C, the expected chlorin **1.32** was obtained (Scheme 1.8). The product has an interesting and unusual three-dimensional structure.



1.32

Scheme 1.8

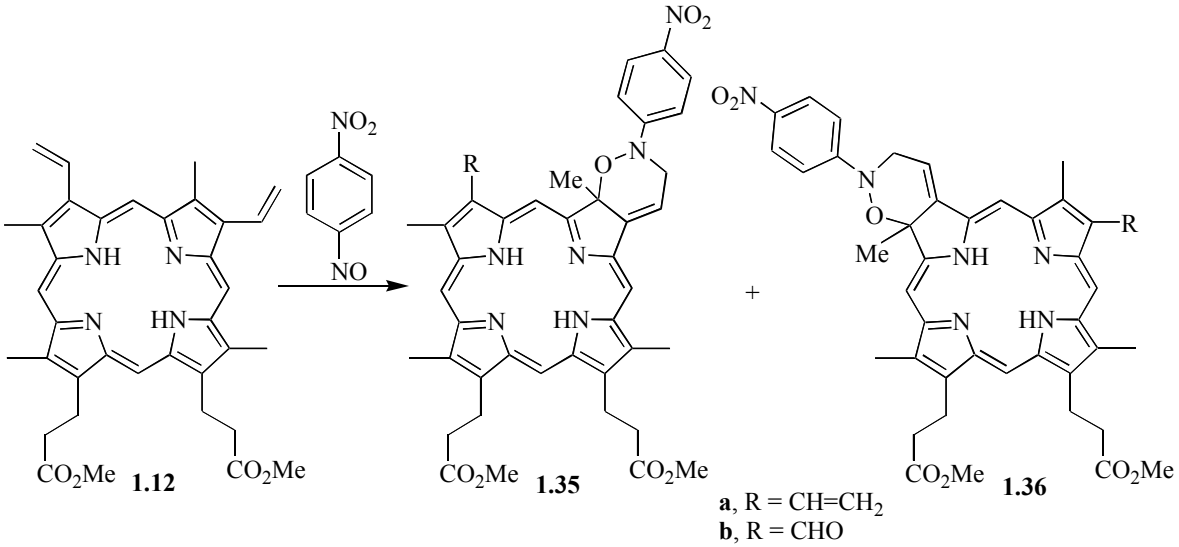
Photoproducts such as **1.34** were obtained in the reaction of Protoporphyrin-IX dimethyl ester **1.12** with singlet oxygen. Their formation was explained *via* the intermediate [4+2] adduct **1.33** (Scheme 1.9).[86] The reaction was referred to occur in either vinylic pyrrolic unit but not in both.



1.12 **1.33** **1.34**

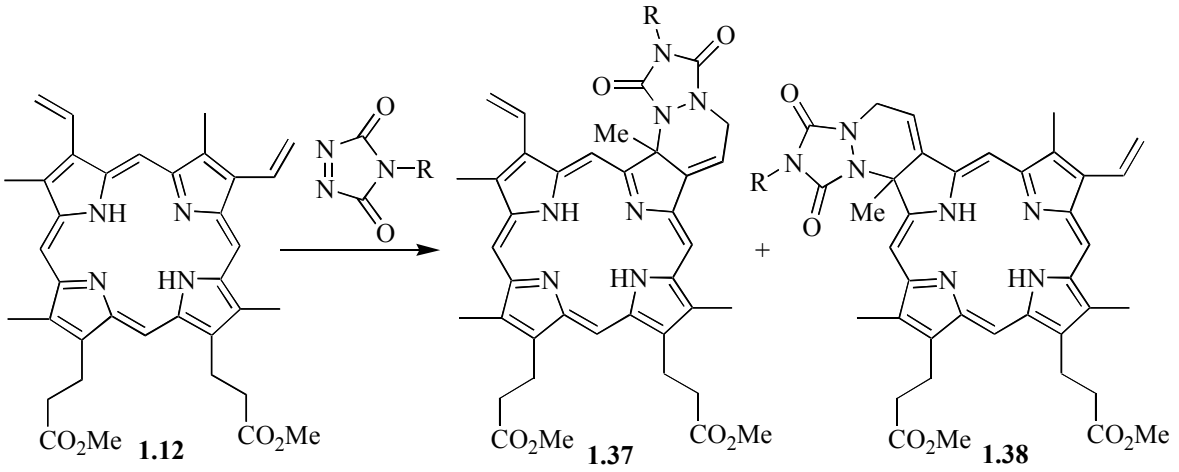
Scheme 1.9

The reactions of porphyrins with heterodienophiles were also explored. Protoporphyrin-IX dimethyl ester **1.12** reacted with substituted nitrosobenzenes to yield the Diels-Alder adducts.[87] However, even with the more reactive ones (with electron-withdrawing substituents) only monoadducts **1.35a** and **1.36a** were obtained (Scheme 1.10). In the presence of an excess of the dienophile, the formyl-monoadducts **1.35b** and **1.36b** were also obtained.



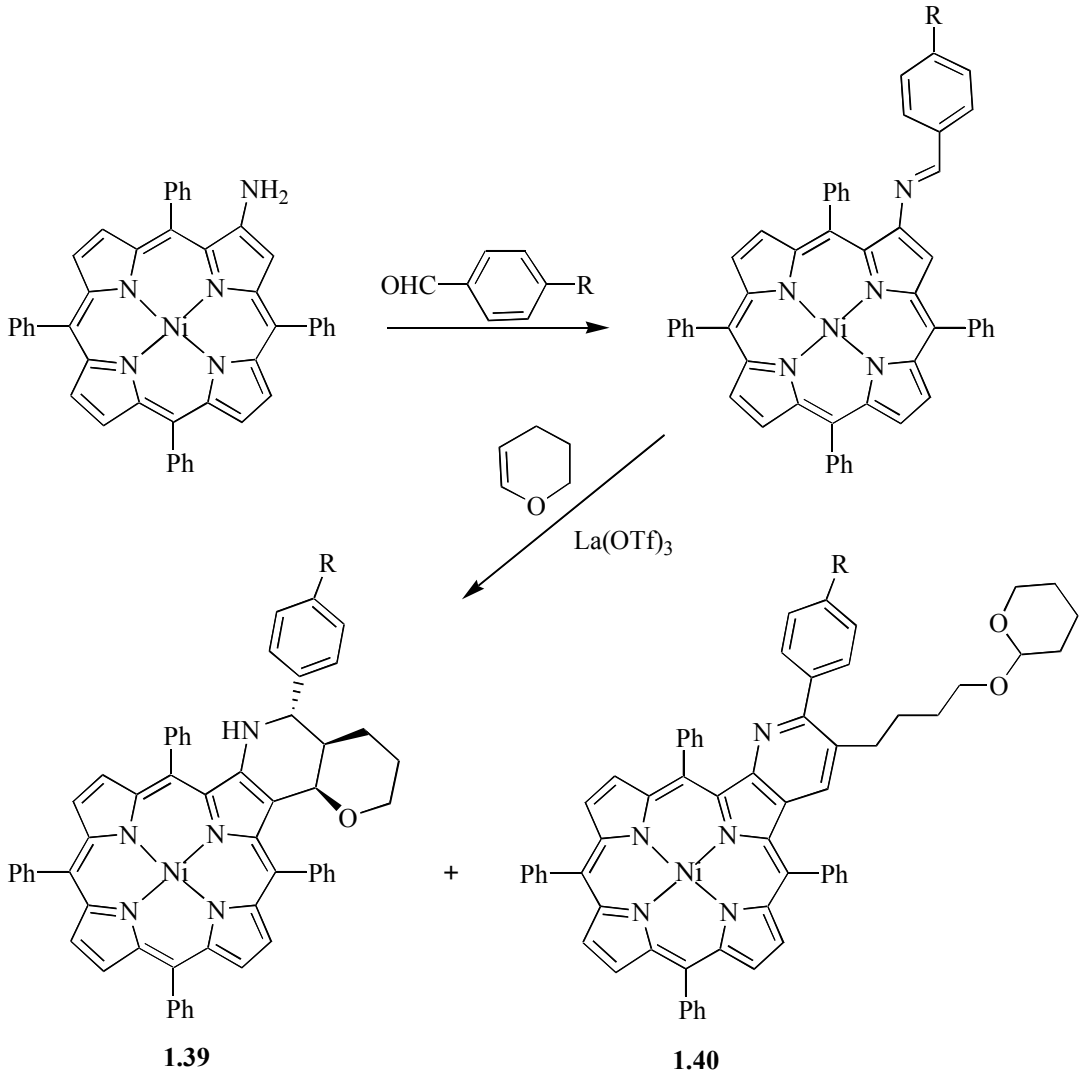
Scheme 1.10

The reaction of Protoporphyrin-IX dimethyl ester **1.12** with azo dienophiles such as 1,2,4-triazoline-3,5-dione was also reported (Scheme 1.11).[88] The [4+2] mono-adducts **1.37** and **1.38** were obtained.



Scheme 1.11

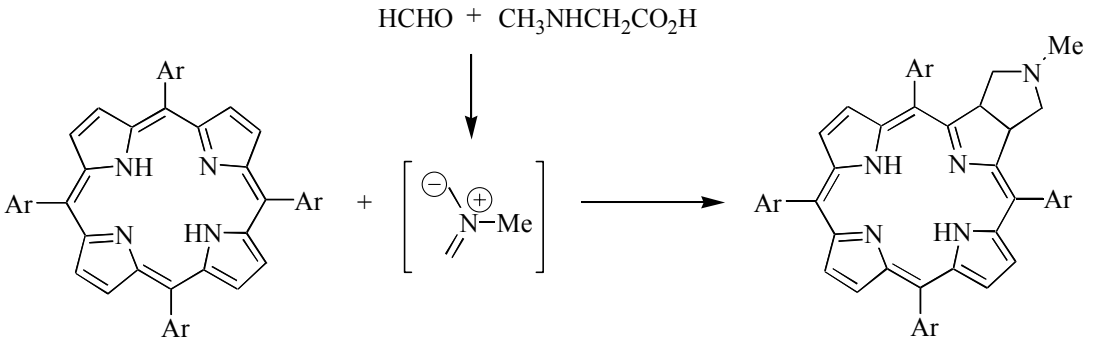
The reactivity of β-imino derivatives of *meso*-tetraphenylporphyrin as heterodienes was also investigated.[89] For instance, in the presence of $La(OTf)_3$ as a Lewis acid, it reacted with 3,4-dihydro-2*H*-pyran to afford tetrahydropyridine-fused porphyrins **1.39** and pyridoporphyrins **1.40** (Scheme 1.12).



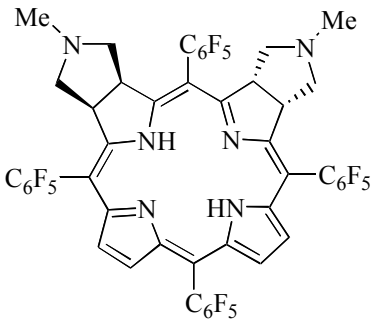
Scheme 1.12

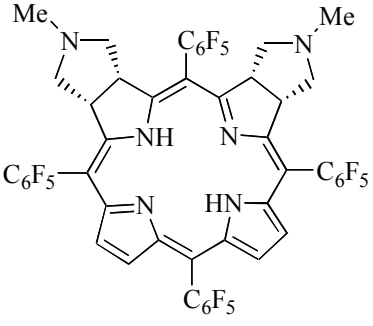
1.2.3: [3+2] Cycloaddition reactions

The Aveiro group has also reported the 1,3-dipolar cycloaddition reactions of porphyrins with azomethine ylides in refluxing toluene.[90] Chlorins **1.41** were isolated as main products in those reactions (Scheme 1.13). For the electron-deficient TPFPP, bis-adducts – isobacteriochlorins **1.42** were also isolated, the '*trans*' one **1.42a** being the major product. Different amino acids can be used successfully as precursors of different azomethine ylides.

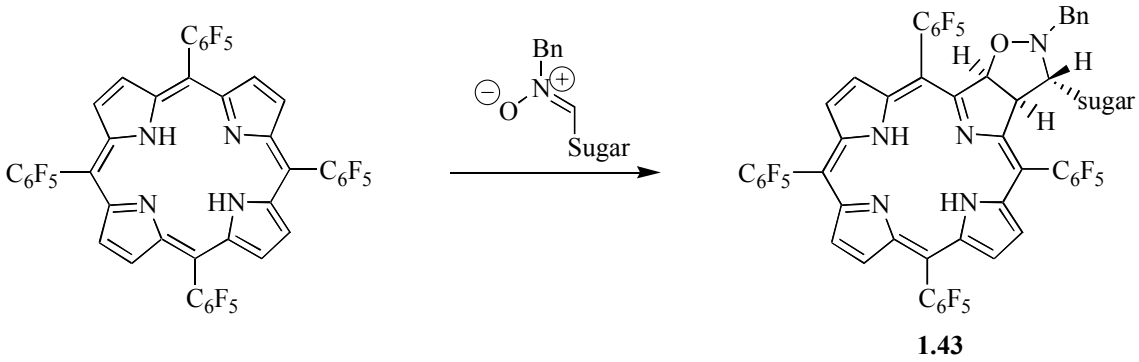


Scheme 1.13



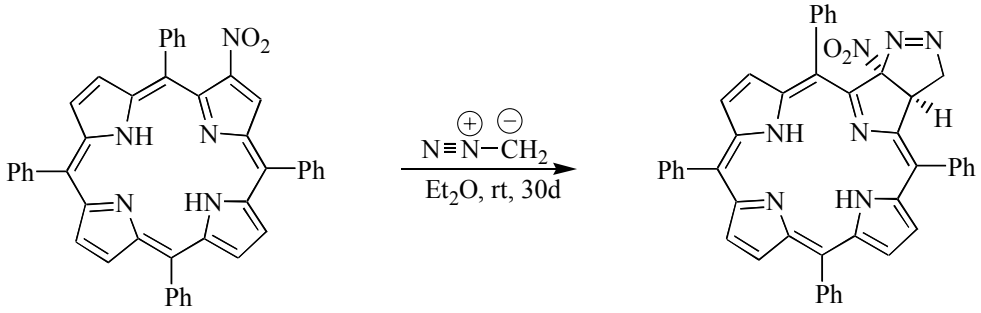


The reaction of porphyrins with nitrones also gave the expected monoadducts and, in some cases, bis-adducts of bacteriochlorins type were also isolated. For example, the reaction of *meso*-tetrakis(pentafluorophenyl)porphyrin with sugar nitrones also gave the expected chlorins **1.43** (Scheme 1.14).[91]



Scheme 1.14

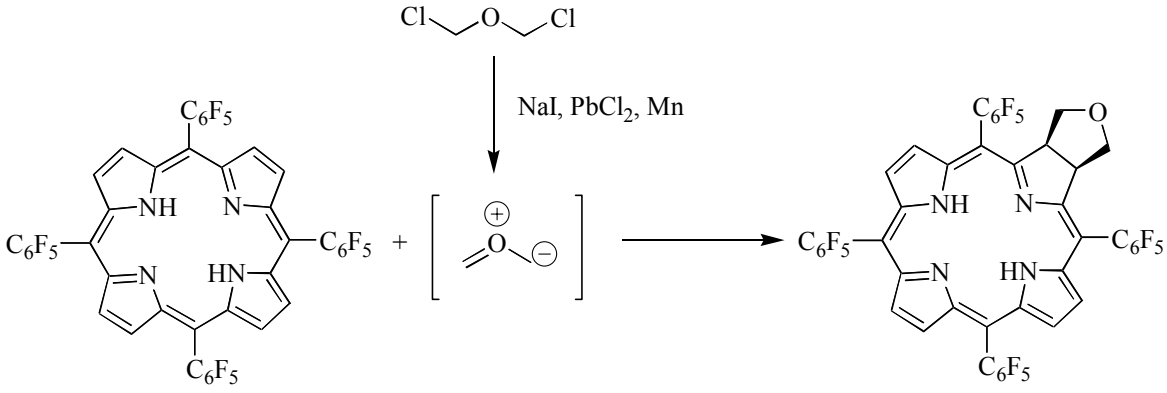
Our group has reported the 1,3-dipolar cycloaddition reactions of β-nitro-*meso*-tetraphenylporphyrin with diazomethane, at room temperature, to afford pyrazoline-fused chlorin **1.44** (Scheme 1.15).[92a] Later, Dolphin *et al.* have reported quite similar results from the reaction of diazomethane with TPFPP.[92b]



1.44

Scheme 1.15

The same Canadian group has also reported the 1,3-dipolar cycloaddition reactions of porphyrins with carbonyl ylides.[93] Tetrahydrofuran adducts such as **1.45** were obtained from these [3+2] cycloaddition reactions (Scheme 1.16).



1.45

Scheme 1.16

Meanwhile, the Aveiro group has also reported the 1,5-electrocyclic ring closure reactions of β-formylporphyrin derivatives.[94] Pyrrolo[3,4-*b*]porphyrin **1.46** was obtained from an intramolecular reaction of Ni β-formyl TPP with *N*-methylglycine (Scheme 1.17).

1.46

Scheme 1.17

Porphyrin-based photosensitizers are being synthesized as potential candidates for photodynamic therapy (PDT) in our laboratories. For this purpose the most interesting porphyrin derivatives are those which have strong absorptions in the visible region near or above 650 nm, and these include chlorins, bacteriochlorins, and porphyrins with extended π-systems. Cycloaddition reactions of porphyrins can provide an approach to synthesize those new and potential photosensitizers. The results described in this thesis are included in such work targets.

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Chapter 2: 1,3-Dipolar cycloaddition reactions of *meso*-tetraarylporphyrins with azomethine ylides

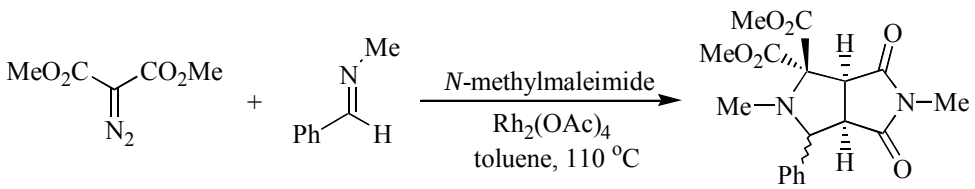
2.1: Generation of azomethine ylides

1,3-Dipolar [3+2] cycloadditions are an effective method for the synthesis of five-membered heterocycles.[1] One of the most important classes for 1,3-dipolar cycloaddition involves azomethine ylides. For the construction of nitrogen-containing five-membered heterocycles, the use of such ylides represent the most simple and efficient method.

Generation of the ylide, usually *in situ*, followed by the dipolarophile attack, furnishes pyrrolidines and related heterocycles. There are many methods for the preparation of azomethine ylides, these can be stabilized if an adjacent electron-withdrawing group is present or non-stabilized if that is not the case. The most general and reliable methods commonly used for the generation of azomethine ylides are shown in the following reactions.

2.1.1: From carbenes and catalytically generated metal carbenoids

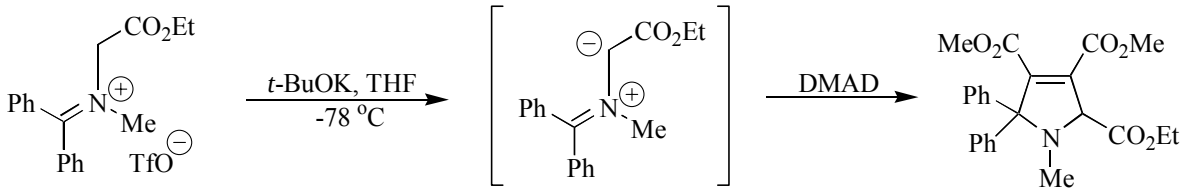
Azomethine ylides can be generated by the reaction of carbenes or carbenoids with imines. Usually, this method is used for the generation of stabilized azomethine ylides (Scheme 2.1).[2]



Scheme 2.1

2.1.2: Deprotonation of iminium salts

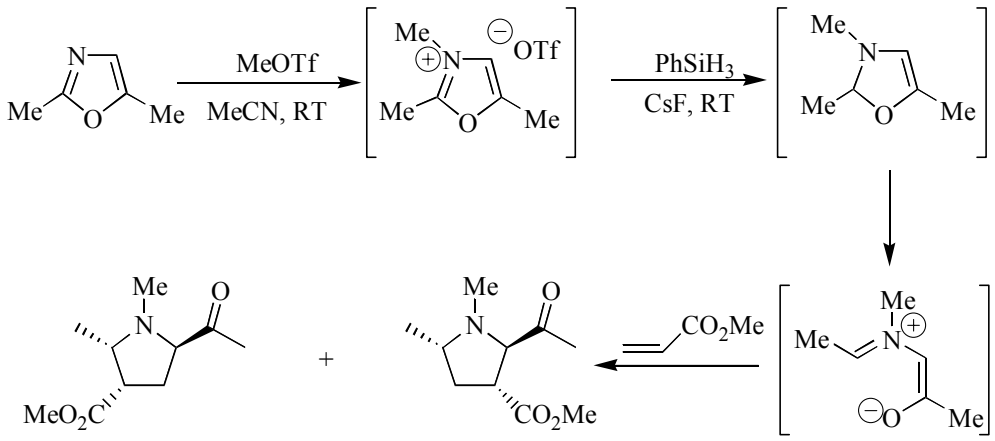
One of the most obvious methods for the preparation of an azomethine ylide involves the direct deprotonation of an iminium salt with a suitable base (Scheme 2.2).[3] In general, an electron-withdrawing substituent is required to facilitate deprotonation, so the method is restricted to the preparation of stabilized azomethine ylides.



Scheme 2.2

2.1.3: From oxazolines, oxazolidines and oxazolidinones

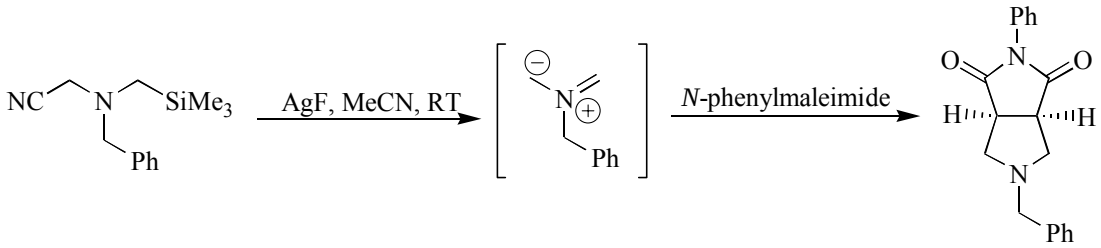
Oxazolium salts[4a] and oxazolidines[4b] and oxazolidinones[4c] are convenient and stable precursors for the generation of stabilized azomethine ylides. Vedejs *et al.* have reported that the reduction of oxazolium salts to give 4-oxazolines which then undergo C-O bond cleavage to deliver stabilized azomethine ylides (Scheme 2.3).[4a]



Scheme 2.3

2.1.4: Desilylation reactions

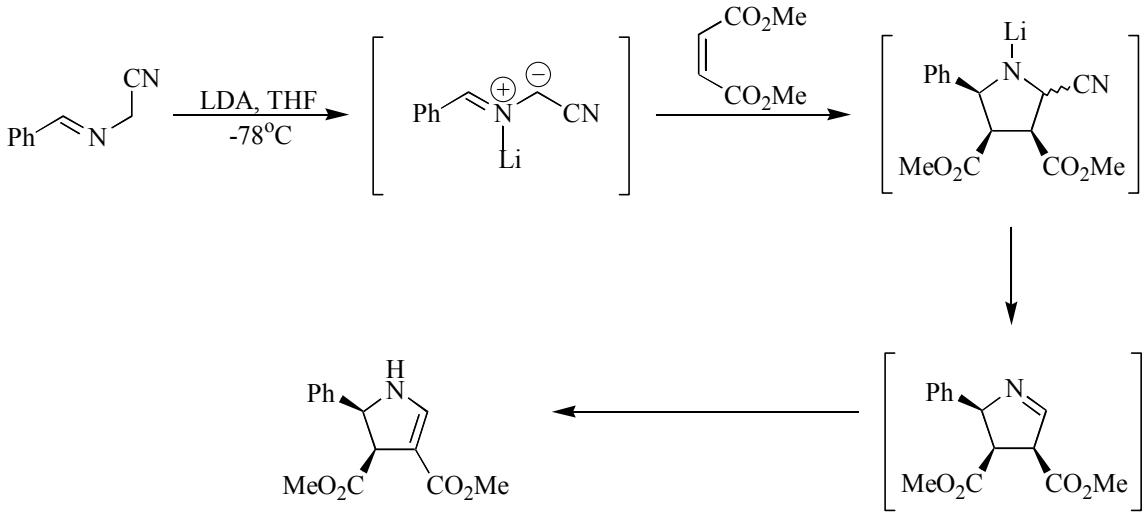
Another method involves the desilylation of an α-silyl imine/iminium compound or an α-silyl amine bearing a good leaving group (Scheme 2.4).[5] It is one of the most popular methods for the generation of non-stabilized azomethine ylides.



Scheme 2.4

2.1.5: Generation of *N*-metallated azomethine ylides

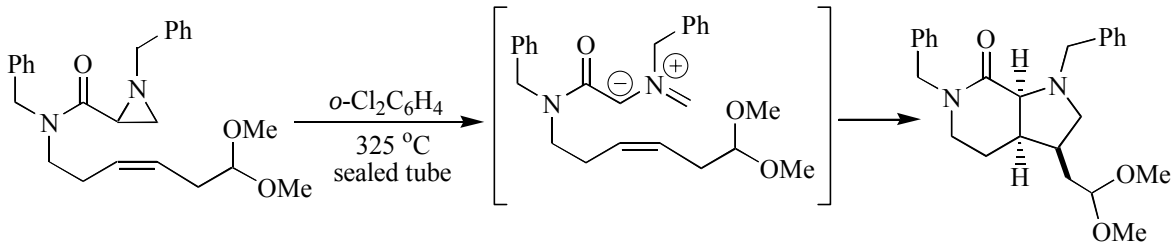
In recent years, *N*-metallated azomethine ylides have been widely used since such species are equivalents to stabilized azomethine ylides (Scheme 2.5).[6]



Scheme 2.5

2.1.6: Ring opening of azirines

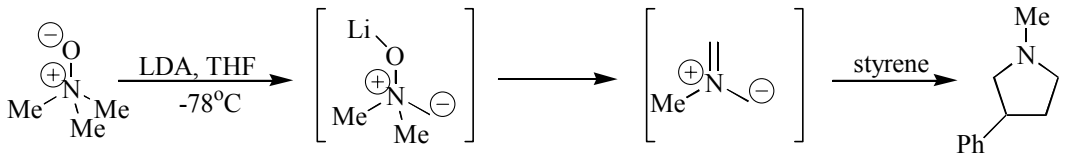
The inherent ring strain of aziridines means that they can be converted into azomethine ylides under appropriate conditions. In general, this method is best one for the generation of stabilized azomethine ylides (Scheme 2.6).[7]



Scheme 2.6

2.1.7: From *N*-oxides of tertiary amines

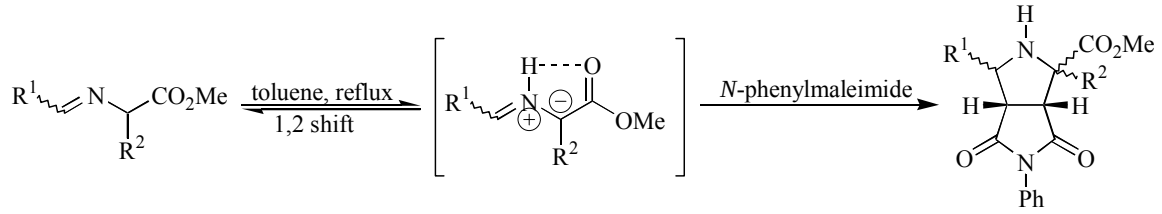
Roussi *et al.* have reported that a tertiary amine *N*-oxide, on treatment with non-nucleophilic strong bases such as lithium diisopropylamide (LDA), generates the non-stabilized azomethine ylide (Scheme 2.7).[8]



Scheme 2.7

2.1.8: 1,2-Prototropic shift of imines

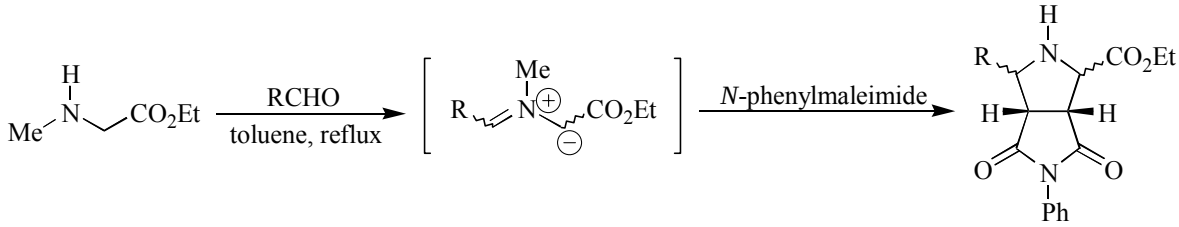
A stabilized azomethine ylide can be generated by 1,2-prototropic shift of an imine generated upon condensation of an aldehyde or ketone with a primary α-amino carbonyl compound (Scheme 2.8).[9]



Scheme 2.8

2.1.9: Condensation of aldehydes and ketones with secondary α-amino carbonyl compounds

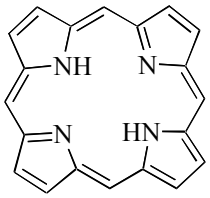
The direct generation of stabilized azomethine ylides by the condensation of carbonyl compounds with secondary α-amino carbonyl compounds has become a popular method (Scheme 2.9).[10]



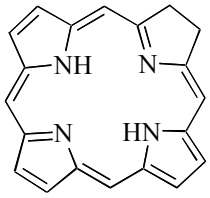
Scheme 2.9

2.2: The reactivity of porphyrins as dipolarophiles

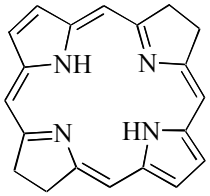
Porphyrins **2.1** are the aromatic macrocycles containing a total of 22 conjugated π electrons, 18 of which are incorporated into the delocalization pathway in accord with Hückel's [4n+2] rule for aromaticity (n = 4). Thus one or two of the peripheral double bonds of porphyrins can undergo addition, reduction, oxidation and pericyclic reactions to form chlorins **2.2**, bacteriochlorins **2.3** or isobacteriochlorins **2.4**, without substantial loss of the macrocyclic aromaticity.



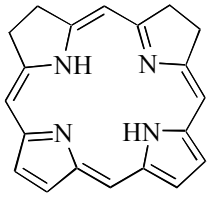
2.1



2.2

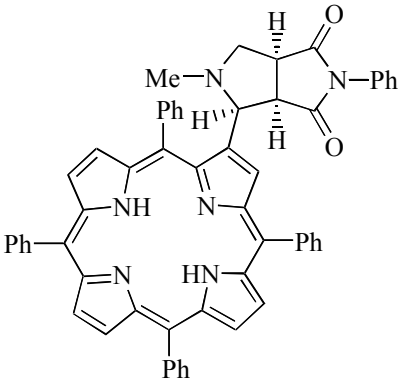


2.3

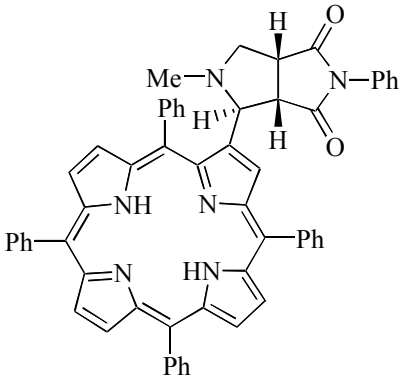


2.4

Azomethine ylides have been used in the synthesis of natural products[11] and functionalization of fullerene C_{60}.[12] The Aveiro group was the first one to report three reactions based on the cycloaddition reactions of porphyrins with azomethine ylides: (a) the 1,3-dipolar cycloaddition reactions of *meso*-tetraarylporphyrins with azomethine ylides to yield chlorins **1.41**;[13] (b) pyrroloporphyrins such as **1.46** were obtained from the 1,5-electrocyclic ring closure reactions of porphyrin azomethine ylides generated from β-formylporphyrins;[14] (c) the porphyrin azomethine ylides generated from β-formylporphyrins also can react with a range of dipolarophiles to yield the corresponding adducts such as **2.5a** and **2.5b**.[15]



2.5a



2.5b

As part of such studies, we have investigated (a) the reactivities of *meso*-tetraarylporphyrins with azomethine ylides; (b) the reactions of A_3B type *meso*-

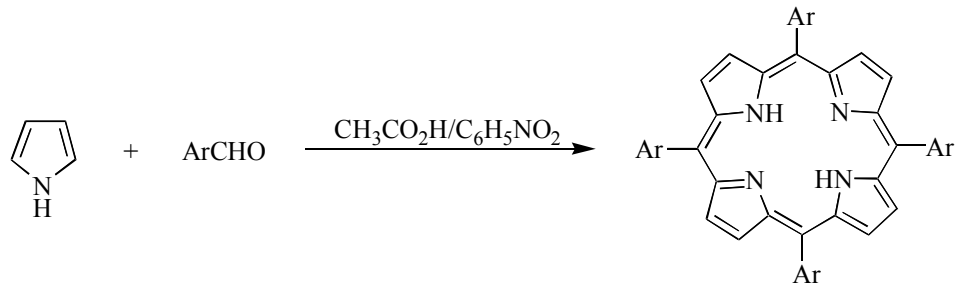
tetraarylporphyrins with azomethine ylides and the site selectivities; (c) the intramolecular 1,3-dipolar reactions involving azomethine ylides generated from *meso*-(*o*-formylphenyl) porphyrins.

2.3: Reactivities of *meso*-tetraarylporphyrins with azomethine ylides

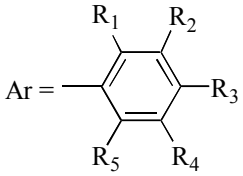
It was planned to look for porphyrins which should have a significant reactivity in the presence of azomethine ylides. Such porphyrins must have electron-withdrawing substituents since it is expected that such feature will make them more reactive in the cycloaddition reactions.

2.3.1: Synthesis of starting porphyrins

Synthesis of starting *meso*-tetraarylporphyrins **2.6a-g** was carried out by acidic condensation of pyrrole with one equivalent of substituted benzaldehydes in a mixture of acetic acid and nitrobenzene at 120 ^{o}C for one hour (Scheme 2.10).[16] After column chromatography (silica gel) using a mixture of chloroform/light petroleum (1:1) as eluent, the reactions afforded porphyrins **2.6a-g** in yields of 6-27%. Unfortunately, the solubilities of some porphyrins, especially **2.6b**, in organic solvents are poor. The structures of the starting porphyrins were confirmed by their UV-Vis and ^{1}H NMR spectra. Porphyrin **2.6a** was obtained in 9% yield. Its UV-Vis spectrum shows absorption bands at λ_{max} 415, 514, 548, 589, and 645 nm. In the ^{1}H NMR spectrum, the protons of *meso*-phenyl groups appear as two multiplets at δ 8.55-8.58 ppm (*para*-H, 4H) and δ 8.71-8.74 ppm (*ortho*-H, 4H), and another four *ortho*-protons appear as a broad singlet at δ 9.09 ppm, four *meta*-protons appear as a triplet at δ 8.00 ppm (*J* 7.9 Hz). The eight β-pyrrolic protons appear as one singlet at δ 8.82 ppm.



2.6

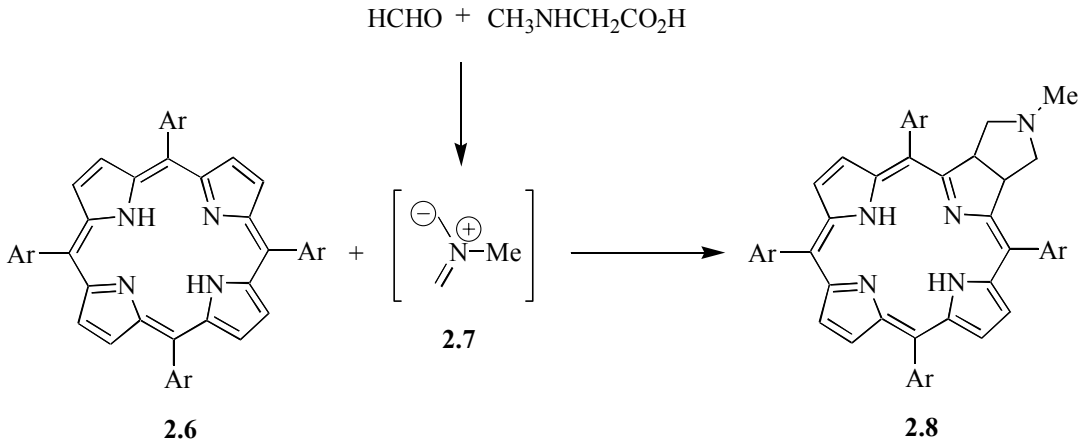


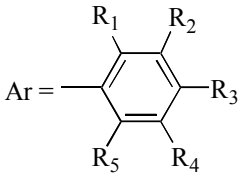
a, $R_1 = R_3 = R_4 = R_5 = H$, $R_2 = NO_2$
b, $R_1 = R_4 = R_5 = H$, $R_2 = NO_2$, $R_3 = Cl$
c, $R_1 = R_2 = R_4 = R_5 = H$, $R_3 = F$
d, $R_1 = R_3 = R_5 = H$, $R_2 = R_4 = F$
e, $R_1 = R_5 = H$, $R_2 = R_3 = R_4 = F$
f, $R_1 = R_2 = R_4 = R_5 = F$, $R_3 = H$
g, $R_1 = R_2 = R_3 = R_4 = R_5 = F$

Scheme 2.10

2.3.2: The reactivity of porphyrins in the cycloaddition reaction with azomethine ylide

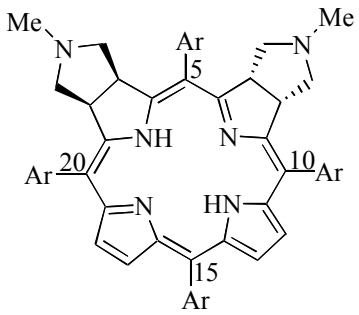
In contrast to the Diels-Alder reactions, the 1,3-dipolar cycloaddition reactions of porphyrins can be performed at mild conditions ranging from room temperature to refluxing in toluene.[17] We performed the reactions of porphyrins with azomethine ylide generated from the condensation of paraformaldehyde with *N*-methylglycine in refluxing toluene for 8 hours (Scheme 2.11). It has been shown that such azomethine ylides are exclusively limited to the aromatic aldehydes or formaldehyde.[18] When an aliphatic aldehyde containing an α-proton is utilized, the resulting ylide can tautomerize to an enamine and react with a second molecule, resulting in a complex mixture. Due to the poor solubilities of some porphyrins, we used an higher volume of solvent (toluene) than that described in the literature. The reaction mixtures were separated by column chromatography (silica gel) using a gradient of $CHCl_3$-light petroleum. Mono-adducts (chlorins **2.8a-g**) and bis-adducts such as isobacteriochlorins **2.9f-g** were isolated and characterized from the cycloaddition reactions. The structures of the new compounds were confirmed by their UV-Vis, ^1H (^{19}F) NMR and mass spectra. The results are presented in Table 2.1.



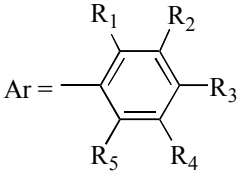


a, $R_1 = R_3 = R_4 = R_5 = H$, $R_2 = NO_2$
b, $R_1 = R_4 = R_5 = H$, $R_2 = NO_2$, $R_3 = Cl$
c, $R_1 = R_2 = R_4 = R_5 = H$, $R_3 = F$
d, $R_1 = R_3 = R_5 = H$, $R_2 = R_4 = F$
e, $R_1 = R_5 = H$, $R_2 = R_3 = R_4 = F$
f, $R_1 = R_2 = R_4 = R_5 = F$, $R_3 = H$
g, $R_1 = R_2 = R_3 = R_4 = R_5 = F$

Scheme 2.11



2.9f,g



f, $R_1 = R_2 = R_4 = R_5 = F$, $R_3 = H$
g, $R_1 = R_2 = R_3 = R_4 = R_5 = F$

Table 2.1 The reactivity of porphyrins in 1,3-dipolar cycloaddition reactions

Recovered starting porphyrins	Mono-adducts	Bis-adducts
2.6a (97%)	**2.8a** (1%)	not observed
2.6b (62%)	**2.8b** (13%)	not observed
2.6c (84%)	**2.8c** (10%)	not observed
2.6d (79%)	**2.8d** (19%)	Trace
2.6e (70%)	**2.8e** (25%)	Trace
2.6f (11%)	**2.8f** (59%)	**2.9f** (14%)
2.6g (29%)	**2.8g** (49%)	**2.9g** (6%)

For the reaction of porphyrin **2.6g**, chlorin **2.8g** was isolated in 49% yield. The UV-Vis spectrum of compound **2.8g** is typical of a chlorin (λ_{max} 653 nm). Its mass spectrum shows intense peaks at *m/z* 1032 ($[M+H]^+$) and 1031 ($[M]^{+\bullet}$) and it confirms that it is a mono-adduct. In the ^{1}H NMR spectrum, a singlet at δ 2.21 ppm, corresponding to the N-C*H*$_3$ protons, and two multiplets at δ 2.53-2.57 and 3.13-3.17 ppm, corresponding to the methylene protons, are observed. Another multiplet at δ 5.26-5.28 ppm is assigned to the resonance of the two β-pyrrolic protons of the reduced ring. In the aromatic region, four of the six β-pyrrolic protons appear as two doublets at δ 8.40 and 8.72 ppm (*J* 4.9 Hz) and a singlet at δ 8.49 ppm for the other two.

The '*trans*' isobacteriochlorin **2.9g** was also isolated from the bis-adduct mixtures as the main product (6% yield). It was identified by the UV-Vis, ^{1}H and ^{19}F NMR and mass spectra. The UV-Vis spectrum of compound **2.9g** shows that it is an isobacteriochlorin (λ_{max} 545 and 586 nm). The mass spectrum shows intense peaks at *m/z* 1089 ($[M+H]^+$) and 1088 ($[M]^{+\bullet}$), confirming that it is a bis-adduct. In the ^{1}H NMR spectrum, a multiplet at δ 2.06-2.17 ppm corresponding to the six N-C*H*$_3$ protons and two pyrrolidine protons, is observed. Two broad singlets at δ 2.27 and 2.86 ppm, and a multiplet at δ 2.62-2.67 ppm corresponding to other six pyrrolidine protons, are also observed. The two NH protons appear as a broad singlet at δ 4.10 ppm, this signal disappeared after shaking with deuterium oxide. The four β-pyrrolic protons of the reduced ring appear as a multiplet at δ 4.39-4.41 ppm. In the aromatic region, the four β-pyrrolic protons appear as two doublets at δ 7.09 (2H, *J* 4.4 Hz) and 7.55 ppm (2H, *J* 4.4 Hz), indicating that it is an isobacteriochlorin, and not a bacteriochlorin. The ^{19}F NMR spectrum shows that its structure must be a symmetrical one – the '*trans*' isobacteriochlorins **2.9g**, not the '*cis*' configuration, since only four signals are observed for *m*-fluorine atoms: one signal for the two *m*-F atoms in the 5-phenyl ring, two signals for the two non-equivalent *m*-F atoms in the equivalent 10- and 20-phenyl rings, and one signal for the two *m*-F atoms in the 15-phenyl ring.

It is evident from the obtained results that the presence of electron-withdrawing atoms in *meso*-aryl groups increases the reactivity of the porphyrin towards azomethine ylide. Porphyrin **2.6f** is more reactive than porphyrin **2.6g**, although **2.6g**, in relation with **2.6f**,

has one fluorine atom more in each *meso*-aryl group. Porphyrin **2.6b** was recovered in 62% from the reaction medium and this might be probably due to its poor solubility.

Chlorins **2.8a-g** have intense absorption bands near or above 650 nm. Most of the second generation photosensitizers for photodynamic therapy (PDT) studied so far are reduced porphyrins with their strong absorptions in the red region of visible spectrum.[19] Besides the PDT treatment of cancer, other diseases such as the age-related macular degeneration are being treated by chlorin derivatives; other applications (*e.g.*, as new drugs against microorganisms) are being considered.

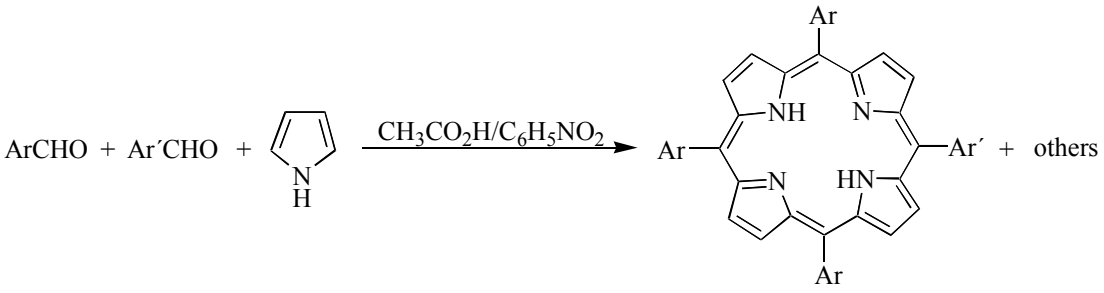
2.4: A_3B type *meso*-tetraarylporphyrins as dipolarophiles and the site selectivities

A_3B type *meso*-tetraarylporphyrins have two non-equivalent peripheral double bonds. Since the reactivity of *meso*-tetraarylporphyrins in 1,3-dipolar cycloaddition reaction with azomethine ylide is dominated by the electronic effect of the *meso*-aryl groups, then the peripheral double bonds of A_3B type porphyrins must show different reactivities. We then decided to investigate the reactions of A_3B type *meso*-tetraarylporphyrins with azomethine ylides and to look for the site selectivities.

2.4.1: Synthesis of starting porphyrins

The starting A_3B type *meso*-tetraarylporphyrins were prepared using an acid-catalyzed mixed aldehyde synthesis (Scheme 2.12). The aryl group B is more electron-deficient than the aryl group A. Six porphyrins (*meso*-aryl groups: AAAA, AAAB, AABB, ABAB, ABBB, BBBB) were generated from these reactions. The desired porphyrins **2.10a-c** were separated from the statistical mixture of products in 6-11% yields. The structures of porphyrins **2.10a-c** were confirmed by their UV-Vis, ^{1}H NMR and mass spectra. Porphyrin **2.10a** was isolated in 8% yield by column chromatography. In the ^{1}H NMR spectrum, a

singlet at δ 4.11 ppm corresponding to protons of three methoxy groups is observed (chemical shifts of the three methoxy groups are the same). The *meso*-phenyl groups appear as a multiplet at δ 7.27-7.33 (*meta*-H, 6H) and a doublet at δ 8.13 ppm (*ortho*-H, 6H, *J* 8.6 Hz). The eight β-pyrrolic protons appear as two doublets at δ 8.75 (2H, *J* 4.7 Hz) and 8.96 ppm (2H, *J* 4.7 Hz), and an AB spin system at δ 8.87 and 8.88 ppm (4H, *J* 4.9 Hz). The mass spectrum shows intense peaks at *m/z* 795 ($[M+H]^+$) and 794 ($[M]^{+\bullet}$), confirming the structure as a A_3B porphyrin **2.10a**.



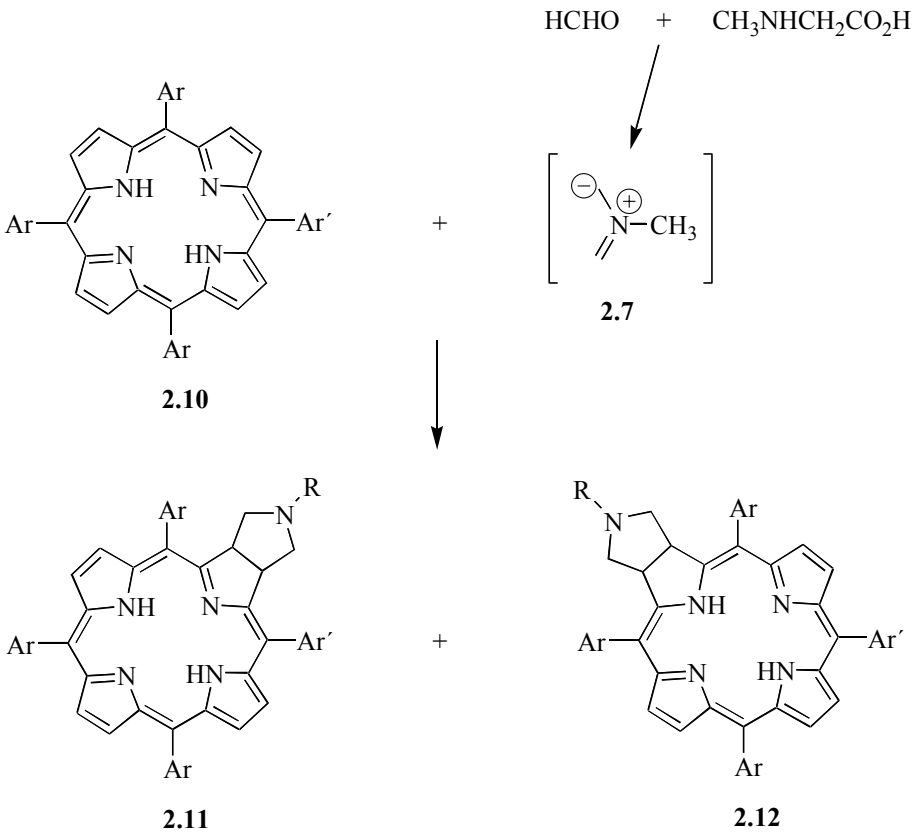
2.10

a, Ar = 4-$CH_3OC_6H_4$, Ar′ = C_6F_5
b, Ar = Ph, Ar′ = C_6F_5
c, Ar = Ph, Ar′ = 4-$NO_2C_6H_4$
(A = Ar; B = Ar′)

Scheme 2.12

2.4.2: 1,3-Dipolar cycloaddition reactions of A_3B type *meso*-tetraarylporphyrins and the site selectivities

1,3-Dipolar cycloaddition reactions of A_3B type *meso*-tetraarylporphyrins **2.10a-c** with azomethine ylide were carried out in refluxing toluene (Scheme 2.13). For example, porphyrin **2.10a** reacted with azomethine ylide **2.7**, generated *in situ* from the condensation of paraformaldehyde with *N*-methylglycine. After 56 hours, two isomeric chlorins **2.11a** (the one with higher R_f value on TLC, 30% yield) and **2.12a** (the one with lower R_f value on TLC, 9% yield) were isolated together with unchanged starting porphyrin **2.10a** (48%) by column chromatography (silica gel).



a, Ar = 4-$MeOC_6H_4$, Ar′ = C_6F_5
b, Ar = Ph, Ar′ = C_6F_5
c, Ar = Ph, Ar′ = 4-$NO_2C_6H_4$

Scheme 2.13

These structures for **2.11a** and **2.12a** were deduced from their UV-Vis, ^1H, ^{19}F and NOESY NMR and mass spectra. The UV-Vis spectra show that both compounds **2.11a** and **2.12a** are chlorins (Fig. 2.1, **2.11a** λ_{max} 647 nm and **2.12a** λ_{max} 652 nm). Due to the steric and electronic effects, the highest wavelength bands show those small differences.[20] The mass spectra of the two products show that **2.11a** and **2.12a** are mono-adducts ($[M+H]^+$ = 852). From ^1H NMR spectra of **2.11a** and **2.12a**, we can see the fine differences, the two β-pyrrolic protons of the reduced ring of **2.11a** appear as two quartets at δ 5.11 (*J* 8.5 Hz) and 5.40 ppm (*J* 8.5 Hz), but they appear as one multiplet at δ 5.33-5.43 ppm in **2.12a**; that means the chemical surroundings of these two β-pyrrolic protons in **2.11a** are more different than in **2.12a**. These results are in agreement with the structures of **2.11a** and **2.12a**. The ^{19}F NMR spectra also confirm the structures of the two isomers: the two *m*-fluorine atoms of **2.11a** appear as two multiplets at δ -185.16 to -185.00 ppm and δ -184.81

to -184.67 ppm, the two *o*-fluorine atoms appear as two double doublets at δ -161.26 (*J* 7.1 and 24.0 Hz) and -159.15 ppm (*J* 7.1 and 24.0 Hz); for **2.12a**, the two *m*-fluorine atoms appear as one multiplet at δ -186.16 to -185.87 ppm, the two *o*-fluorine atoms appear as two close double doublets at δ -160.84 (*J* 8.5 and 25.4 Hz) and -160.63 ppm (*J* 8.5 and 22.6 Hz), thus confirming that the chemical surroundings of fluorine atoms in **2.11a** are more different between themselves than those in **2.12a**. NOESY NMR spectra can also confirm both structures. There is a NOE effect between pyrrolidine protons at δ 2.35-2.46 ppm and the two *ortho*-protons of one adjacent *meso*-phenyl group at δ 7.84 ppm (doublet, *J* 8.6 Hz) in **2.11a**. However in **2.12a** a cross peak is observed between pyrrolidine protons at δ 2.29-2.36 ppm and four *ortho*-protons of two adjacent *meso*-phenyl groups at δ 7.83-7.89 ppm.

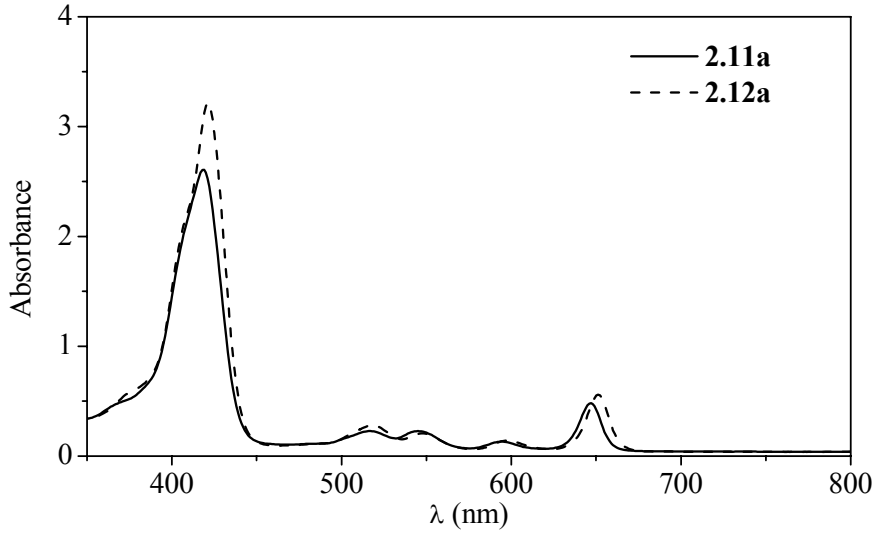
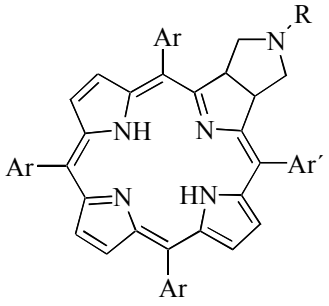


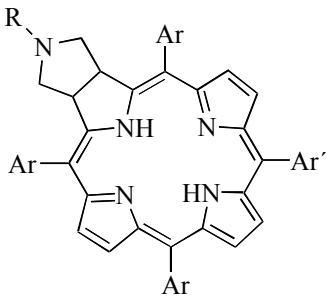
Figure 2.1: UV-Vis spectra of isomeric chlorins 2.11a and 2.12a

Two other porphyrins and another 1,3-dipole (products **2.11d** and **2.12d**) were also investigated, the results are presented in Table 2.2. From TLC, we found that the major mono-adducts **2.11a-d** are less polar than the minor mono-adducts **2.12a-d**. For the isomeric chlorins **2.11c** and **2.12c**, the polarities are very similar on TLC, the mixture of EtOAc-light petroleum is the best solvent for separation of two isomers (in other cases, mixtures of $CHCl_3$-light petroleum were used). Obviously, the 1,3-dipolar cycloaddition reaction of azomethine ylides with A_3B type *meso*-tetraarylporphyrins **2.10a-c** is site selective; the aryl group with stronger electron-withdrawing effect directs the reaction to

the neighbouring pyrrolic unit. The site selectivity follows the electron-withdrawing order of the *meso*-aryl groups: 4-$MeOC_6H_4$ < Ph ≈ 4-$NO_2C_6H_4$ < C_6F_5. Two 1,3-dipoles gave similar results (**2.11b**, **2.12b** and **2.11d**, **2.12d**). To our surprise, the starting porphyrin **2.10a** is more reactive than **2.10b**, although **2.10b** is more electron-deficient than **2.10a**.



2.11d



2.12d

Ar = Ph, Ar′ = C_6F_5, R = Bn

Table 2.2 Comparative site selectivity of A_3B type *meso*-tetraarylporphyrins with azomethine ylides

Recovered porphyrin	Yield of isomeric mono-adducts		Ratio **2.11**:**2.12**
2.10a (48%)	**2.11a** (30%)	**2.12a** (9%)	77:23
2.10b (81%)	**2.11b** (9%)	**2.12b** (4%)	69:31
2.10c (85%)	**2.11c** (6%)	**2.12c** (5%)	55:45
2.10b (83%)	**2.11d** (10%)	**2.12d** (4%)	71:29

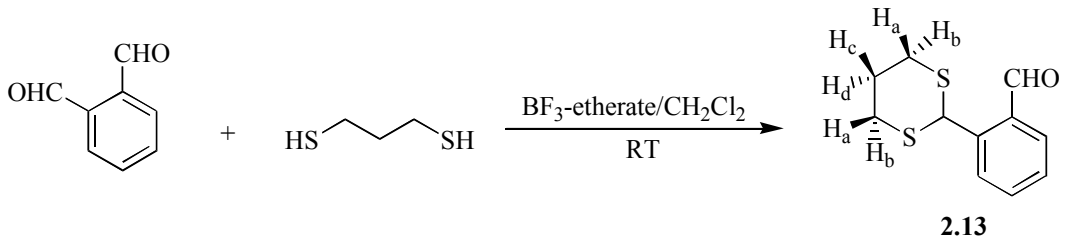
2.5: Intramolecular 1,3-dipolar cycloaddition reactions of *meso*-(*o*-formylphenyl)porphyrins

Although in the macrocycle the rotation of *meso*-phenyl rings is restricted, sometimes, the rotational barriers are not very high.[21] Gottwald and Ullman were the first to report the rate constant for the rotation of *meso*-tetrakis(*o*-hydroxyphenyl)porphyrin, which is 1.5×10^{-5} s^{-1} in methanol at 23 ^oC.[22] The four atropisomers (α,α,α,α; α,α,α,β; α,α,β,β; α,β,α,β) of *meso*-tetrakis(*o*-aminophenyl)porphyrin were found to be reasonably stable

and readily separated by column chromatography at room temperature. Heating in refluxing toluene caused equilibration of the mixture of atropisomers.[23] Recently, a 1,5-electrocyclic ring closure reaction from the ylide derived from a β-formylporphyrin was reported by our group.[14] We expected that the novel *meso*+β fused porphyrins could be obtained by the intramolecular 1,3-dipolar cycloadditon reactions of *meso*-(*o*-formylphenyl)porphyrins; followed by subsequent oxidative aromatization, that is, the reactions between the peripheral double bonds of porphyrins and 1,3-dipoles at *ortho*-position of the *meso*-phenyl ring.

2.5.1: Synthesis of starting porphyrins

The aldehyde required for the preparation of *meso*-(*o*-formylphenyl)porphyrins is the mono-protected *o*-phthalaldehyde **2.13**. The reaction conditions of Lindsey method are compatible with a wide variety of functional and protecting groups. But Lindsey found that under some conditions 1,3-dioxane-protected aldehydes are also unstable in the Lindsey procedure.[24] Therefore, mono dithianyl-protected *o*-phthalaldehyde **2.13** was prepared in 65% yield from the reaction of *o*-phthalaldehyde with one equivalent of propane-1,3-dithiol catalyzed by BF_3-etherate in dichloromethane at room temperature (Scheme 2.14).[25]



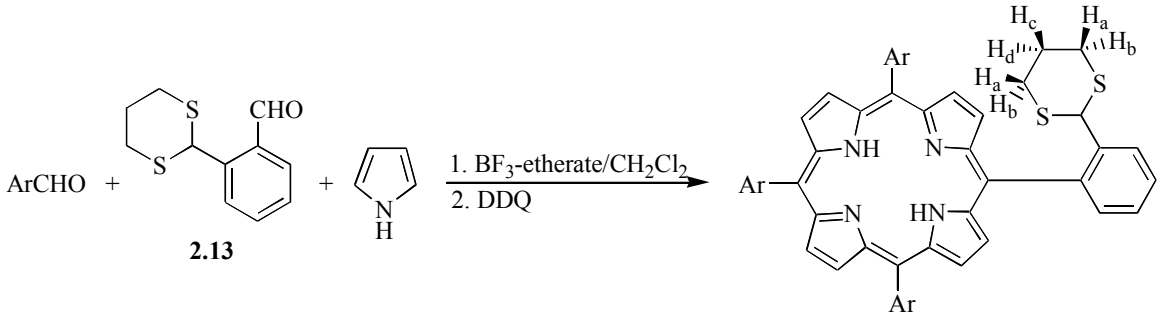
2.13

Scheme 2.14

The structure of compound **2.13** was confirmed by ^{1}H NMR and mass spectra. The protons of the protecting group appear as four multiplets at δ 1.87-2.00 (1H, H_d), 2.16-2.24 (1H, H_c), 2.88-2.96 (2H, H_b) and 3.09-3.19 ppm (2H, H_a). The protected α-proton appears as a singlet at δ 6.24 ppm, the free formyl proton appears as another singlet at δ 10.39 ppm.

The phenyl protons appear as two double doublets at δ 7.47 (*J* 1.1 and 7.6 Hz) and 7.58 ppm (*J* 1.4 and 7.6 Hz), and two double triplets at δ 7.76 (*J* 1.1 and 7.6 Hz) and 7.83 ppm (*J* 1.4 and 7.6 Hz). The EI-MS shows a peak at *m/z* 224 ($[M]^{+\bullet}$).

The porphyrins **2.14** were prepared using an acid-catalyzed mixed aldehyde synthesis at room temperature using the Lindsey method (Scheme 2.15). Porphyrin **2.14a** was isolated in 16% yield, but **2.14b** and **2.14c** were both obtained in only 4% yield. TLC revealed that each reaction mixture was very complicated presumably because other macrocycles were also generated. These might be the expanded porphyrins since it has been shown that electron-deficient aldehydes can give rise to expanded porphyrins.[26] The structures of the porphyrins **2.14** were confirmed by their UV-Vis, ^{1}H NMR and mass spectra. The mass spectrum of **2.14a** shows intense peaks at *m/z* 895 ($[M+H]^+$) and 894 ($[M]^{+\bullet}$), which confirm that it is the dithianyl-protected *meso*-(*o*-formylphenyl)porphyrin **2.14a**. In the ^{1}H NMR spectrum, the protons of the dithianyl protecting group appear as three multiplets at δ 1.55-1.69 (2H), 1.84-1.94 (2H) and 2.33-2.38 ppm (2H), the protected α-H appears as a singlet at δ 4.76 ppm. The protons of the *meso*-aryl groups appear as one double triplet at δ 7.57 ppm (1H, *J* 1.2 and 7.7 Hz), one double doublet at δ 8.21 ppm (1H, *J* 0.8 and 7.7 Hz) and one multiplet at δ 7.77-7.98 ppm (8H). The eight β-pyrrolic protons appear as two AB spin systems at δ 8.87 (4H, *J* 4.8 Hz) and 8.95 ppm (4H, *J* 4.7 Hz).



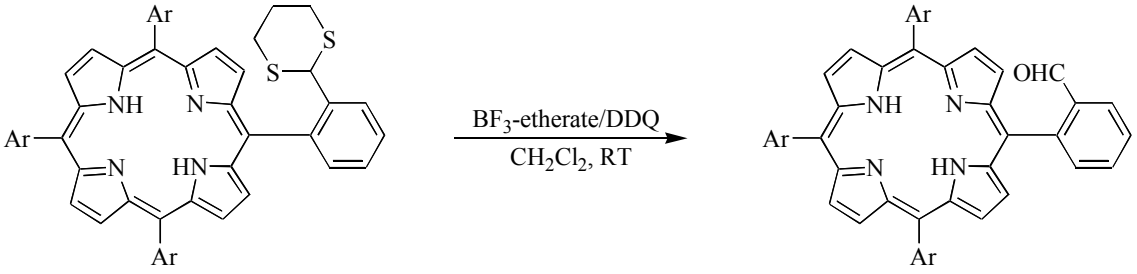
2.14

a, Ar = 3,4,5-$F_3C_6H_2$
b, Ar = 2,3,6-$F_3C_6H_2$
c, Ar = C_6F_5

Scheme 2.15

The cleavage of the dithioacetal group to the corresponding carbonyl compounds is an important reaction in synthetic organic chemistry. For this transformation, various

procedures such as selenium (IV) oxide,[27] sulfuryl chloride[28] and DDQ[29] oxidative cleavages have been reported. DDQ mediated cleavage is the most cheap and convenient method. Deprotection reactions were achieved by using 5 equivalents of DDQ catalyzed by BF_3-etherate in dichloromethane at room temperature (Scheme 2.16).[30] Although this procedure is similar to the conditions used in the synthesis of porphyrins **2.14**, the concentrations and equivalents of DDQ and BF_3-etherate are different. Porphyrins **2.15** were generated in good yields (**2.15a,b** both 86% yields, **2.15c** 60% yield). The structures of the porphyrins **2.15** were confirmed by their UV-Vis, ^{1}H NMR and mass spectra. The mass spectrum of **2.15a** shows intense peaks at *m/z* 805 ($[M+H]^+$) and 804 ($[M]^{+\bullet}$) confirming that it is the deprotected *meso*-(*o*-formylphenyl)porphyrin **2.15a**. Its UV-Vis spectrum is similar to that of TPP. In the ^{1}H NMR spectrum, the protons of the *meso*-aryl groups appear as three multiplets at δ 7.82-8.00 (m, 8H), 8.22-8.25 (m, 1H) and 8.41-8.44 ppm (m, 1H). The eight β-pyrrolic protons appear as two doublets at δ 8.83 (2H, *J* 4.8 Hz) and 8.85 ppm (2H, *J* 4.8 Hz) and an AB spin system at δ 8.89 ppm (4H, *J* 4.8 Hz). The aldehyde proton appears as a singlet at δ 9.46 ppm.



2.14

2.15

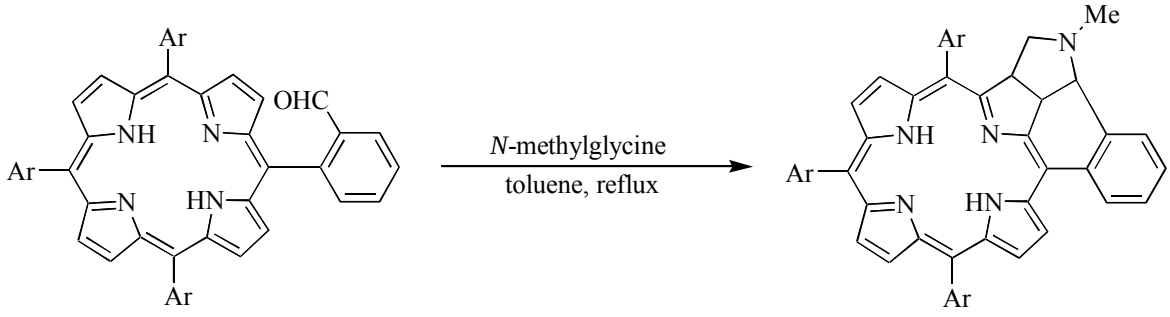
a, Ar = 3,4,5-$F_3C_6H_2$
b, Ar = 2,3,6-$F_3C_6H_2$
c, Ar = C_6F_5

Scheme 2.16

2.5.2: Intramolecular 1,3-dipolar cycloaddition reactions

We investigated the possibility to obtain compounds **2.16** by intramolecular 1,3-dipolar cycloaddition reactions. Porphyrins **2.15a,c** were reacted with 5 equivalents of *N*-

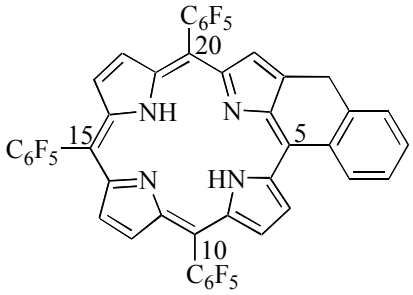
methylglycine in refluxing toluene for 6 hours (Scheme 2.17). TLC revealed that most porphyrin **2.15a** was unchanged and being contaminated with a number of complicated products in small amounts. The starting porphyrin **2.15a** was recovered in 70% yield and the expected chlorin **2.16a** was obtained in only 2% yield! The UV-Vis spectrum of **2.16a** is typical of a chlorin (λ_{max} 671 nm) and the mass spectrum shows intense peaks at *m/z* 832 ($[M+H]^+$) and 831 ($[M]^{+\bullet}$) confirming that it is the expected adduct. The reaction of porphyrin **2.15c** with *N*-methylglycine, under the same reaction conditions, afforded the expected chlorin **2.16c** in 6% yield. Compound **2.17** was also obtained in 10% yield.



2.15 **2.16**

a Ar = 3,4,5-$F_3C_6H_2$
c Ar = C_6F_5

Scheme 2.17

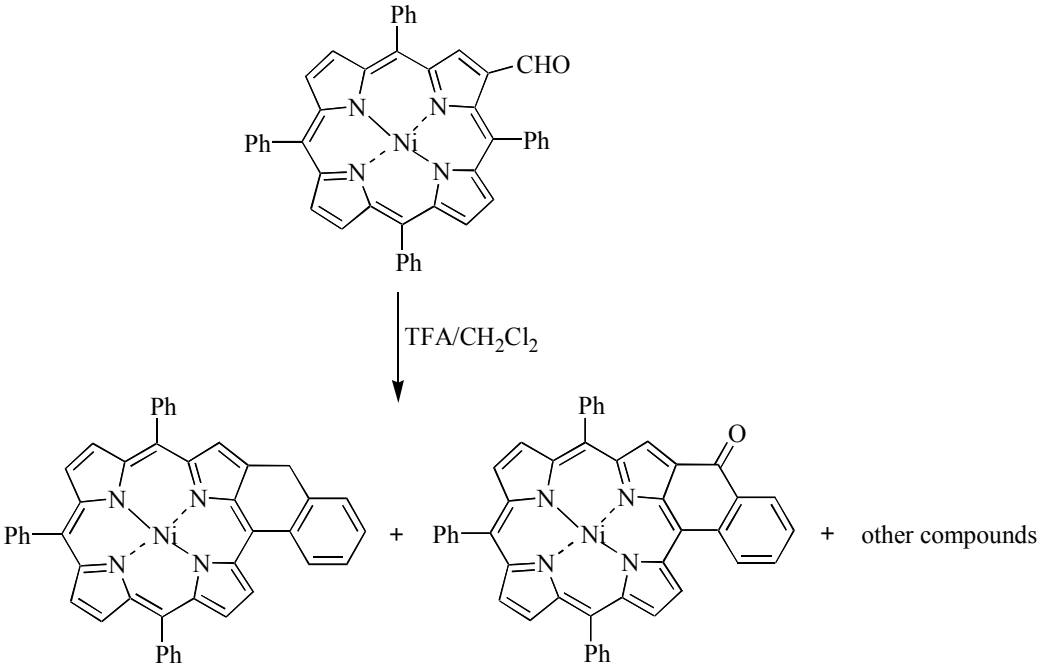


2.17

The structures of the porphyrins **2.16c** and **2.17** were deduced from their UV-Vis, ^{1}H NMR and mass spectra. The UV-Vis spectrum shows **2.16c** is typical of a chlorin (λ_{max} 675 nm). The mass spectrum shows intense peaks at *m/z* 940 ($[M+H]^+$) and 939 ($[M]^{+\bullet}$), confirming that it is a 1,3-dipolar cycloaddition adduct. In the ^{1}H NMR spectrum, the N-CH_3 protons appear as a singlet at δ 2.42 ppm. A triplet at δ 2.87 ppm (*J* 9.8 Hz) and two doublets at δ 3.18 (*J* 9.8 Hz) and 3.98 ppm (*J* 4.6 Hz), corresponding to three pyrrolidine ring protons are observed. One double doublet at δ 4.75 ppm (*J* 4.6 and 7.7 Hz) and a

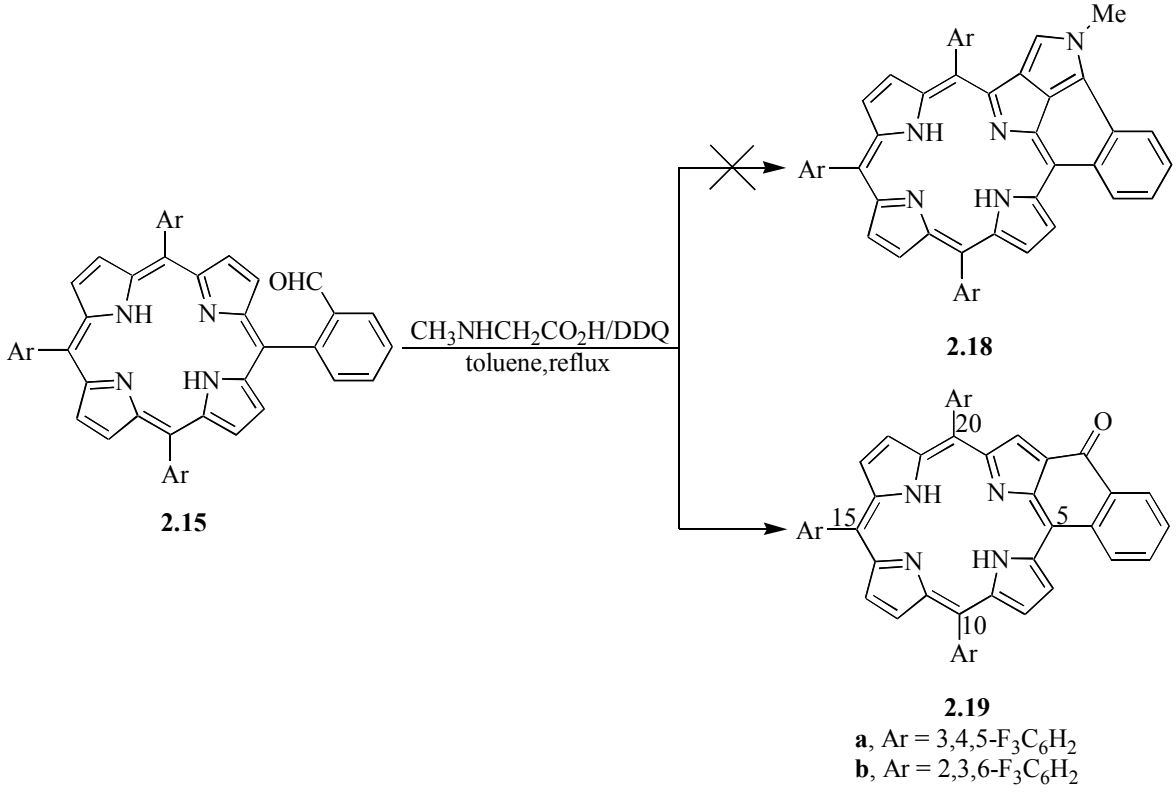
multiplet at δ 4.92-4.98 ppm are assigned to the resonance of the two β-pyrrolic protons of the reduced ring. The four β-pyrrolic protons appear as four doublets at δ 8.21 (*J* 4.9 Hz), 8.36 (*J* 4.6 Hz), 8.40 (*J* 4.6 Hz), and 9.10 ppm (*J* 4.9 Hz). A multiplet at δ 8.54-8.62 ppm, corresponding to another two β-pyrrolic protons and a phenyl proton is observed. Another three phenyl protons appear as a double doublet at δ 7.77 ppm (*J* 1.2 and 7.5 Hz), and two double triplets at δ 7.64 (*J* 1.0 and 7.5 Hz) and 7.86 ppm (*J* 1.2 and 7.5 Hz). The mass spectrum of **2.17** shows intense peaks at *m/z* 897 ($[M+H]^+$) and 896 ($[M]^{+\bullet}$), confirming that it is a methylene-bridged porphyrin. In the ^1H NMR spectrum, the methylene protons appear as a singlet at δ 5.16 ppm. Four β-pyrrolic protons appear as a singlet at δ 8.55 ppm (H-2) and three doublets at δ 8.13 (*J* 4.6 Hz), 8.19 (*J* 5.2 Hz), and 9.15 ppm (*J* 4.6 Hz). A multiplet at δ 8.29-8.41 ppm corresponding to the remaining β-pyrrolic protons and a phenyl proton is observed. The other three phenyl protons appear as a triplet at δ 7.80 (*J* 7.7 Hz), a double triplet at δ 7.96 (*J* 1.2 and 7.7 Hz), and a doublet at 9.38 ppm (*J* 7.7 Hz).

It is not surprising to obtain the porphyrin **2.17** since such methylene-bridged porphyrins were obtained in the acid-catalyzed intramolecular cyclization reaction of β-formylporphyrins (Scheme 2.18).[31b,c] It has been reported that the reaction of arenecarbaldehydes with arenes gives a complex mixture of products.[32] The cyclization side reaction can give an indication why this reaction is complicated.



Scheme 2.18

We tried to prepare the novel π-extended porphyrins **2.18a,b** from one-pot reactions of porphyrins **2.15a,b** with *N*-methylglycine and DDQ (Scheme 2.19). The green intramolecular cyclization reaction products **2.19a,b** were obtained instead of the 1,3-dipolar reaction compounds **2.18a,b**. The cyclization compound **2.19a** was also generated in low yield without *N*-methylglycine. Such keto-bridged porphyrins have been reported in the cyclization reactions of β-formylporphyrins (Scheme 2.18);[31] they were also obtained in high yields under oxidative conditions.[31e]

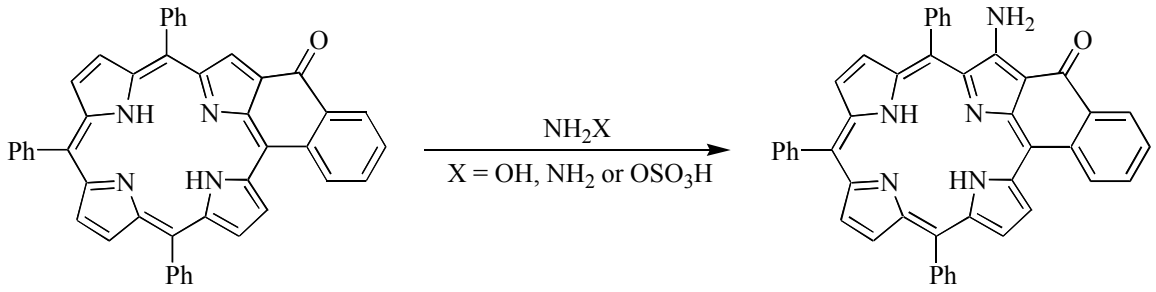


Scheme 2.19

The structures of the porphyrins **2.19a,b** were established by their UV-Vis, ^{1}H NMR and mass spectra. Porphyrin **2.19a** was isolated in 36% yield (11% yield without *N*-methylglycine). Its UV-Vis spectrum shows intense red shift of both Soret and Q bands (λ_{max} 378, 460, 531, 575, 628, 729 nm) relatively to **2.15a**, confirming that it is a porphyrin with an extended π-system. The mass spectrum shows intense peaks at *m/z* 803 ($[M+H]^+$) and 802 ($[M]^{+\bullet}$), 2 Da less than the value corresponding to **2.15a**, confirming that it is an oxidative coupling compound. In the ^{1}H NMR spectrum, a multiplet at δ 7.67-7.79 ppm corresponding to the six protons of the *meso*-3,4,5-trifluorophenyl groups and a proton of

the fused phenyl group is observed. Another three protons of the fused phenyl group appear as a triplet at δ 7.43 ppm (*J* 7.6 Hz) and two doublets at δ 8.16 (*J* 7.6 Hz) and 8.37 ppm (*J* 7.6 Hz). The seven β-pyrrolic protons appear as a singlet at δ 9.09 ppm (H-2), two doublets at δ 8.55 (1H, *J* 4.9 Hz) and 9.28 ppm (1H, *J* 4.8 Hz) and a multiplet at δ 8.59-8.65 ppm (4H).

Callot found that keto-bridged porphyrin **2.20** is a stable ketone for the condensation with amine derivatives.[31d,e] The aminated compound **2.21** was isolated from those reactions (Scheme 2.20). Its formation can explain why we did not obtain porphyrins **2.18** since then it will be difficult to generate 1,3-dipoles from **2.19** *via* condensation with *N*-methylglycine.



2.20 **2.21**

Scheme 2.20

2.6: Conclusion

The reactivity of 1,3-dipolar cycloaddition reactions of symmetrical *meso*-tetraarylporphyrins with azomethine ylides is dominated by the electronic effect of the *meso*-aryl groups. The presence of electron-withdrawing atoms or groups in *meso*-aryl groups increases the reactivity of the porphyrin towards azomethine ylides. We have developed an easy way to synthesize chlorins, which are potentially useful for PDT treatment.

1,3-Dipolar cycloaddition of azomethine ylides with unsymmetrical A_3B type *meso*-tetraarylporphyrins is site selective; the aryl group with the stronger electron-withdrawing effect directs the reaction to the neighbouring pyrrolic unit. The site selectivity follows the

electron-withdrawing order of *meso*-aryl groups: 4-$CH_3OC_6H_4$ < Ph ≈ 4-$NO_2C_6H_4$ < C_6F_5. Regioisomeric chlorins were obtained in those reactions.

Attempted synthesis of π-extended porphyrins **2.18** *via* intramolecular reactions of *meso*-(*o*-formylphenyl)porphyrins with *N*-methylglycine followed by subsequent oxidative aromatizations was unsuccessful due to the intramolecular cyclization side reaction.

2.7: Experimental Section

2.7.1: General

Melting points were measured on a Reichert Thermovar apparatus fitted with a microscope and are uncorrected. ^{1}H and ^{19}F spectra were recorded on a Bruker Avance 300 spectrometer at 300.13 and 282.37 MHz, respectively. $CDCl_3$ was used as solvent and TMS as internal reference; the chemical shifts are expressed in δ (ppm) and the coupling constants (*J*) in Hertz [Hz]. Unequivocal ^{1}H assignments were made with aid of 2D COSY ($^{1}H/^{1}H$) and NOESY spectra (mixing time of 800 ms). FAB Mass spectra and HRMS spectra were recorded on VG AutoSpec Q and M mass spectrometers using $CHCl_3$ as solvent and 3-nitrobenzyl alcohol (NBA) as matrix. ESI HRMS spectra were recorded on APEX III FT-ICR mass spectrometer. The UV-Vis spectra were recorded on a Uvikon spectrophotometer using $CHCl_3$ as solvent. Elemental analyses were performed in Leco 932 and Leco 999 CHN analyzers. Column chromatography was carried out using silica gel (Merck, 35-70 mesh). Preparative thin-layer chromatography was carried out on 20 × 20 cm glass plates coated with Merck 60 silica gel (2 mm thick). Analytical TLC was carried out on precoated sheets with silica gel (Merck 60, 0.2 mm thick). *Meso*-tetrakis(pentafluophenyl)porphyrin was prepared in our Lab. by a colleague.

2.7.2: 1,3-Dipolar cycloaddition reactions of symmetric *meso*-tetraarylporphyrins with azomethine ylides

2.7.2.1: *Meso*-tetrakis(3-nitrophenyl)porphyrin 2.6a[33]

A solution of 3-nitrobenzaldehyde (2.18 g, 14.4 mmol) in glacial acetic acid (100 mL) and nitrobenzene (75 mL) was heated at 120 ^{o}C. Pyrrole (1 mL, 14.4 mmol) was added dropwise within 15 minutes. The temperature was maintained at 120 ^{o}C for 45 minutes.

The solution was cooled down to room temperature and kept overnight. The solvents were distilled under vacuum. The residue was washed with light petroleum (3 × 20 mL) and the mixture separated by column chromatography (silica gel) using a mixture of chloroform/light petroleum (1:1) as eluent, affording porphyrin **2.6a** (0.27 g, 9% yield).[16]

UV-Vis ($CHCl_3$) λ_{max} (% rel. intensity) 415 (100%), 514 (12%), 548 (4%), 589 (4%), 645 (2%) nm.
^{1}H NMR ($CDCl_3$) δ: -2.83 (s, 2H, N*H*), 8.00 (t, 4H, Ph-H_{meta}, *J* 7.9 Hz), 8.55-8.58 (m, 4H, Ph-H_{para}), 8.71-8.74 (m, 4H, Ph-H_{ortho}), 8.82 (s, 8H, *β*-H), 9.09 (br s, 4H, Ph-H_{ortho}).

2.7.2.2: *Meso*-tetrakis(4-chloro-3-nitrophenyl)porphyrin 2.6b[34]

A solution of 4-chloro-3-nitrobenzaldehyde (2.67 g, 14.4 mmol) in glacial acetic acid (100 mL) and nitrobenzene (75 mL) was heated at 120 ^oC. Pyrrole (1 mL, 14.4 mmol) was added dropwise within 15 minutes. The temperature was maintained at 120 ^oC for 45 minutes. The solution was cooled down to room temperature and kept overnight. The solvents were distilled under vacuum. The residue was washed with light petroleum (3 × 20 mL) and the mixture separated by column chromatography (silica gel) using a mixture of chloroform/light petroleum (1:1) as eluent, affording porphyrin **2.6b** (0.57 g, 17% yield).

UV-Vis ($CHCl_3$) λ_{max} (% rel. intensity) 414 (100%), 514 (9%), 548 (4%), 589 (4%), 656 (2%) nm.
^{1}H NMR ($CDCl_3$/TFA) δ: 8.27-8.34 (m, 4H, Ph-H_{meta}), 8.70-8.76 (m, 4H, Ph-H_{ortho}), 8.86 (s, 8H, *β*-H), 9.05-9.08 (m, 4H, Ph-H_{ortho}).

2.7.2.3: *Meso*-tetrakis(4-fluorophenyl)porphyrin, 2.6c[35]

A solution of 4-fluorobenzaldehyde (1.54 mL, 14.4 mmol) in glacial acetic acid (100 mL) and nitrobenzene (75 mL) was heated at 120 ^{o}C. Pyrrole (1 mL, 14.4 mmol) was added dropwise within 15 minutes. The temperature was maintained at 120 ^{o}C for 45 minutes. The solution was cooled down to room temperature and kept overnight. The solvents were distilled under vacuum. The residue was washed with light petroleum (3 × 20 mL) and the mixture separated by column chromatography (silica gel) using a mixture of chloroform/light petroleum (1:1) as eluent, affording porphyrin **2.6c** (0.66 g, 27% yield).

UV-Vis ($CHCl_3$) λ_{max} (% rel. intensity) 414 (100%), 514 (8%), 549 (3%), 589 (2%), 646 (2%) nm.
^{1}H NMR ($CDCl_3$/TFA) δ: 7.77 (t, 8H, Ph-H$_{meta}$, J 8.4 Hz), 8.54 (dd, 8H, Ph-H$_{ortho}$, J_{HH} 8.4 Hz and J_{HF} 5.3 Hz), 8.73 (s, 8H, β-H).

2.7.2.4: *Meso*-tetrakis(3,5-difluorophenyl)porphyrin, 2.6d[36]

A solution of 3,5-difluorobenzaldehyde (2.05 g, 14.4 mmol) in glacial acetic acid (100 mL) and nitrobenzene (75 mL) was heated at 120 ^{o}C. Pyrrole (1 mL, 14.4 mmol) was added dropwise within 15 minutes. The temperature was maintained at 120 ^{o}C for 45 minutes. The solution was cooled down to room temperature and kept overnight. The solvents were distilled under vacuum. The residue was washed with light petroleum (3 × 20 mL) and the mixture separated by column chromatography (silica gel) using a mixture of chloroform/light petroleum (1:1) as eluent, affording porphyrin **2.6d** (0.17 g, 6% yield).

UV-Vis ($CHCl_3$) λ_{max} (% rel. intensity) 411 (100%), 511 (13%), 544 (4%), 587 (5%), 642 (2%) nm.
^{1}H NMR ($CDCl_3$) δ: -2.98 (s, 2H, N*H*), 7.31 (tt, 4H, Ph-H$_{para}$, J_{HH} 2.3 Hz and J_{HF} 8.9 Hz), 7.73-7.79 (m, 8H, Ph-H$_{ortho}$), 8.89 (s, 8H, β-H).

2.7.2.5: *Meso*-tetrakis(3,4,5-trifluorophenyl)porphyrin, 2.6e

A solution of 3,4,5-trifluorobenzaldehyde (1.60 mL, 14.4 mmol) in glacial acetic acid (100 mL) and nitrobenzene (75 mL) was heated at 120 ^{o}C. Pyrrole (1 mL, 14.4 mmol) was added dropwise within 15 minutes. The temperature was maintained at 120 ^{o}C for 45 minutes. The solution was cooled down to room temperature and kept overnight. The solvents were distilled under vacuum. The residue was washed with light petroleum (3 × 20 mL) and the mixture separated by column chromatography (silica gel) using a mixture of chloroform/light petroleum (1:1) as eluent, affording porphyrin **2.6e** (0.62 g, 21% yield).

mp > 300 ˚C.
UV-Vis ($CHCl_3$) λ_{max} (log ε) 413 (5.28), 510 (4.25), 543 (3.63), 586 (3.76), 643 (3.43) nm.
^{1}H NMR ($CDCl_3$) δ: -3.03 (s, 2H, N*H*), 7.84 (dd, 8H, Ph-H_{ortho}, J_{HF} 6.6 and 7.4 Hz), 8.88 (s, 8H, *β*-H).
MS (FAB^+) 831 $(M+H)^+$, 830 $M^{+\bullet}$.

2.7.2.6: *Meso*-tetrakis(2,3,5,6-tetrafluorophenyl)porphyrin, 2.6f[37]

A solution of 2,3,5,6-tetrafluorobenzaldehyde (0.33 mL, 2.8 mmol) in glacial acetic acid (20 mL) and nitrobenzene (15 mL) was heated at 120 ^{o}C. Pyrrole (0.20 mL, 2.8 mmol) was added dropwise within 15 minutes. The temperature was maintained at 120 ^{o}C for 45 minutes. The solution was cooled down to room temperature and kept overnight. The solvents were distilled under vacuum. The residue was washed with light petroleum (3 × 20 mL) and the mixture separated by column chromatography (silica gel) using a mixture of chloroform/light petroleum (1:1) as eluent, affording porphyrin **2.6f** (0.07 g, 11% yield).

UV-Vis ($CHCl_3$) λ_{max} (% rel. intensity) 408 (100%), 506 (11%), 540 (3%), 583 (4%), 636 (1%) nm.
^{1}H NMR ($CDCl_3$) δ: -2.88 (s, 2H, N*H*), 7.58-7.70 (m, 4H, Ph-H), 8.93 (s, 8H, *β*-H).

2.7.2.7: 1,3-Dipolar cycloaddition reaction of porphyrin 2.6a with azomethine ylide 2.7

A toluene (25 mL) solution of porphyrin **2.6a** (20 mg), paraformaldehyde (8 mg, 10 equiv.) and *N*-methylglycine (23 mg, 10 equiv.) was heated at reflux for 8 hours under a nitrogen atmosphere. The reaction mixture was cooled down to room temperature, the solvent was evaporated under vacuum, and the residue was subjected to column chromatography (silica gel) using a gradient of chloroform-light petroleum as eluent. The first fraction to be collected was unchanged starting porphyrin **2.6a** (19.4 mg, 97%), then, the second fraction isolated was the new compound chlorin **2.8a** (0.2 mg, 1% yield).

mp > 300 ˚C.
UV-Vis ($CHCl_3$) λ_{max} (% rel. intensity) 424 (100%), 517 (11%), 543 (8%), 598 (6%), 652 (23%) nm.
^{1}H NMR ($CDCl_3$) δ: -1.84 (s, 2H, N*H*), 2.58 (s, 3H, NCH_3), 2.78-2.96 (m, 2H, pyrrolidine-H), 3.40-3.59 (m, 2H, pyrrolidine-H), 5.74-5.81 (m, 2H, reduced *β*-H), 7.92-8.00 (m, 4H, Ph-H), 8.22-8.27 (m, 2H, Ph-H), 8.37-8.48 (m, 6H, *β*-H and Ph-H), 8.60-8.68 (m, 6H, *β*-H and Ph-H), 8.82-8.86 (m, 2H, Ph-H), 8.94-9.00 (m, 2H, Ph-H).
MS (FAB^+) 852 $(M+H)^+$, 851 $M^{+\bullet}$.

2.7.2.8: 1,3-Dipolar cycloaddition reaction of porphyrin 2.6b with azomethine ylide 2.7

A toluene (25 mL) solution of porphyrin **2.6b** (20 mg), paraformaldehyde (7 mg, 10 equiv.) and *N*-methylglycine (19 mg, 10 equiv.) was heated at reflux for 8 hours under a nitrogen atmosphere. The reaction mixture was cooled down to room temperature, the solvent was evaporated under vacuum, and the residue was subjected to column chromatography (silica gel) using a gradient of chloroform-light petroleum as eluent. The

first fraction to be collected was unchanged starting porphyrin **2.6b** (12.3 mg, 62%), then, the second fraction isolated was the new compound chlorin **2.8b** (2.7 mg, 13% yield).

mp > 300 ˚C.

UV-Vis ($CHCl_3$) λ_{max} (% rel. intensity) 424 (100%), 516 (10%), 544 (7%), 599 (5%), 653 (21%) nm.

^{1}H NMR ($CDCl_3$) δ: -1.82 (s, 2H, N*H*), 2.08 (s, 3H, NCH_3), 2.47-2.53 (m, 2H, pyrrolidine-H), 2.92-2.97 (m, 2H, pyrrolidine-H), 5.30-5.39 (m, 2H, reduced *β*-H), 7.93-8.00 (m, 4H, Ph-H_{meta}), 8.13-8.31 (m, 6H, *β*-H and Ph-H_{ortho}), 8.42 (s, 2H, *β*-H), 8.48-8.63 (m, 6H, *β*-H and Ph-H_{ortho}).

MS (FAB^+) 988 $(M+H)^+$, 987 $M^{+\bullet}$.

2.7.2.9: 1,3-Dipolar cycloaddition reaction of porphyrin 2.6c with azomethine ylide 2.7

A toluene (25 mL) solution of porphyrin **2.6c** (20 mg), paraformaldehyde (9 mg, 10 equiv.) and *N*-methylglycine (26 mg, 10 equiv.) was heated at reflux for 8 hours under a nitrogen atmosphere. The reaction mixture was cooled down to room temperature, the solvent was evaporated under vacuum, and the residue was subjected to column chromatography (silica gel) using a gradient of chloroform-light petroleum as eluent. The first fraction to be collected was unchanged starting porphyrin **2.6c** (16.7 mg, 84%), then, the second fraction isolated was the new compound chlorin **2.8c** (2.2 mg, 10% yield).

mp > 300 ˚C.

UV-Vis ($CHCl_3$) λ_{max} (% rel. intensity) 418 (100%), 517 (11%), 544 (9%), 595 (7%), 648 (19%) nm.

^{1}H NMR ($CDCl_3$) δ: -1.79 (s, 2H, N*H*), 2.09 (s, 3H, NCH_3), 2.36-2.42 (m, 2H, pyrrolidine-H), 2.93-2.99 (m, 2H, pyrrolidine-H), 5.29-5.35 (m, 2H, reduced *β*-H), 7.35-7.44 (m, 8H, Ph-H_{meta}), 7.89-7.95 (m, 4H, Ph-H_{ortho}), 8.04-8.08 (m, 4H, Ph-H_{ortho}), 8.24 (d, 2H, *β*-H, *J* 4.9 Hz), 8.42 (s, 2H, *β*-H), 8.59 (d, 2H, *β*-H, *J* 4.9 Hz).

MS (FAB$^+$) 744 $(M+H)^+$, 743 $M^{+\bullet}$.

2.7.2.10: 1,3-Dipolar cycloaddition reaction of porphyrin 2.6d with azomethine ylide 2.7

A toluene (25 mL) solution of porphyrin **2.6d** (20 mg), paraformaldehyde (8 mg, 10 equiv.) and *N*-methylglycine (24 mg, 10 equiv.) was heated at reflux for 8 hours under a nitrogen atmosphere. The reaction mixture was cooled down to room temperature, the solvent was evaporated under vacuum, and the residue was subjected to column chromatography (silica gel) using a gradient of chloroform-light petroleum as eluent. The first fraction to be collected was unchanged starting porphyrin **2.6d** (15.9 mg, 79%), then, the second fraction isolated was the new compound chlorin **2.8d** (4.1 mg, 19% yield).

mp > 300 ˚C.
UV-Vis ($CHCl_3$) λ_{max} (% rel. intensity) 369 (22%), 414 (100%), 513 (10%), 539 (7%), 596 (5%), 649 (22%) nm.
^{1}H NMR ($CDCl_3$) δ: -1.91 (s, 2H, N*H*), 2.14 (s, 3H, NCH_3), 2.43-2.51 (m, 2H, pyrrolidine-H), 2.99-3.08 (m, 2H, pyrrolidine-H), 5.37-5.45 (m, 2H, reduced *β*-H), 7.16-7.27 (m, 4H, Ph-H$_{para}$), 7.49 (d, 2H, Ph-H$_{ortho}$, *J* 8.5 Hz), 7.54 (d, 2H, Ph-H$_{ortho}$, *J* 8.5 Hz), 7.62 (d, 2H, Ph-H$_{ortho}$, *J* 8.4 Hz), 7.68 (d, 2H, Ph-H$_{ortho}$, *J* 8.4 Hz), 8.32 (d, 2H, *β*-H, *J* 4.9 Hz), 8.47 (s, 2H, *β*-H), 8.66 (d, 2H, *β*-H, *J* 4.9 Hz).
MS (FAB$^+$) 816 $(M+H)^+$, 815 $M^{+\bullet}$.

2.7.2.11: 1,3-Dipolar cycloaddition reaction of porphyrin 2.6e with azomethine ylide 2.7

A toluene (25 mL) solution of porphyrin **2.6e** (20 mg), paraformaldehyde (7 mg, 10 equiv.) and *N*-methylglycine (22 mg, 10 equiv.) was heated at reflux for 8 hours under a

nitrogen atmosphere. The reaction mixture was cooled down to room temperature, the solvent was evaporated under vacuum, and the residue was subjected to column chromatography (silica gel) using a gradient of chloroform-light petroleum as eluent. The first fraction to be collected was unchanged starting porphyrin **2.6e** (13.9 mg, 70%), then, the second fraction isolated was the new compound chlorin **2.8e** (5.3 mg, 25% yield).

UV-Vis ($CHCl_3$) λ_{max} (% rel. intensity) 368 (22%), 416 (100%), 512 (10%), 539 (6%), 596 (4%), 649 (21%) nm.
^{1}H NMR ($CDCl_3$) δ: -1.94 (s, 2H, N*H*), 2.17 (s, 3H, NCH_3), 2.48-2.54 (m, 2H, pyrrolidine-H), 3.04-3.07 (m, 2H, pyrrolidine-H), 5.38-5.43 (m, 2H, reduced *β*-H), 7.55-7.80 (m, 8H, Ph-H_{ortho}), 8.31 (d, 2H, *β*-H, *J* 4.9 Hz), 8.45 (s, 2H, *β*-H), 8.65 (d, 2H, *β*-H, *J* 4.9 Hz).
MS (FAB^+) 888 $(M+H)^+$, 887 $M^{+\bullet}$.

2.7.2.12: 1,3-Dipolar cycloaddition reaction of porphyrin 2.6f with azomethine ylide 2.7

A toluene (25 mL) solution of porphyrin **2.6f** (20 mg), paraformaldehyde (7 mg, 10 equiv.) and *N*-methylglycine (20 mg, 10 equiv.) was heated at reflux for 8 hours under a nitrogen atmosphere. The reaction mixture was cooled down to room temperature, the solvent was evaporated under vacuum, and the residue was subjected to column chromatography (silica gel) using a gradient of chloroform-light petroleum as eluent. The first fraction to be collected was unchanged starting porphyrin **2.6f** (2.2 mg, 11%), then, the second fraction isolated was the new compound chlorin **2.8f** (12.5 mg, 59% yield). The isobacteriochlorin **2.9f** (3.3 mg, 14% yield) was isolated in the third fraction.

2.8f:
UV-Vis ($CHCl_3$) λ_{max} (% rel. intensity) 404 (100%), 504 (12%), 530 (4%), 598 (4%), 652 (30%) nm.

^{1}H NMR ($CDCl_3$) δ: -1.78 (s, 2H, N*H*), 2.22 (s, 3H, NCH_3), 2.54-2.60 (m, 2H, pyrrolidine-H), 3.14-3.19 (m, 2H, pyrrolidine-H), 5.28-5.32 (m, 2H, reduced *β*-H), 7.49-7.62 (m, 4H, Ph-H), 8.41 (d, 2H, *β*-H, *J* 4.9 Hz), 8.51 (s, 2H, *β*-H), 8.73 (d, 2H, *β*-H, *J* 4.9 Hz).
MS (FAB^+) 960 $(M+H)^+$, 959 $M^{+\bullet}$.

2.9f:
UV-Vis ($CHCl_3$) λ_{max} (% rel. intensity) 382 (100%), 507 (14%), 545 (18%), 587 (25%), 642 (6%) nm.
^{1}H NMR ($CDCl_3$) δ: 2.15 (s, 6H, NCH_3), 2.19-2.30 (m, 2H, pyrrolidine-H), 2.65-2.70 (m, 2H, pyrrolidine-H), 2.87-2.90 (m, 2H, pyrrolidine-H), 3.59-3.72 (m, 2H, pyrrolidine-H), 4.11 (br s, 2H, N*H*), 4.55-4.57 (m, 4H, reduced *β*-H), 7.11 (d, 2H, *β*-H, *J* 4.5 Hz), 7.30-7.44 (m, 4H, Ph-H), 7.57 (d, 2H, *β*-H, *J* 4.5 Hz).
MS (FAB^+) 1017 $(M+H)^+$, 1016 $M^{+\bullet}$.

2.7.2.13: 1,3-Dipolar cycloaddition reaction of porphyrin 2.6g with azomethine ylide 2.7

A toluene (25 mL) solution of porphyrin **2.6g** (20 mg), paraformaldehyde (6 mg, 10 equiv.) and *N*-methylglycine (19 mg, 10 equiv.) was heated at reflux for 8 hours under a nitrogen atmosphere. The reaction mixture was cooled down to room temperature, the solvent was evaporated under vacuum, and the residue was subjected to column chromatography (silica gel) using a gradient of chloroform-light petroleum as eluent. The first fraction to be collected was unchanged starting porphyrin **2.6g** (5.8 mg, 29%), then the second fraction isolated was the new compound chlorin **2.8g** (10.4 mg, 49% yield). The isobacteriochlorin **2.9g** (1.4 mg, 6% yield) was isolated in the third fraction.

2.8g:
mp 247-249 ˚C.
UV-Vis ($CHCl_3$) λ_{max} (% rel. intensity) 401 (100%), 504 (14%), 530 (5%), 598 (5%), 653 (41%) nm.

^{1}H NMR ($CDCl_3$) δ: -1.81 (s, 2H, N*H*), 2.21 (s, 3H, NCH_3), 2.53-2.57 (m, 2H, pyrrolidine-H), 3.13-3.17 (m, 2H, pyrrolidine-H), 5.26-5.28 (m, 2H, reduced *β*-H), 8.40 (d, 2H, *β*-H, *J* 4.9 Hz), 8.49 (s, 2H, *β*-H), 8.72 (d, 2H, *β*-H, *J* 4.9 Hz).
MS (FAB^+) 1032 $(M+H)^+$, 1031 $M^{+\bullet}$.

2.9g:
mp 251-253 ˚C.
UV-Vis ($CHCl_3$) λ_{max} (% rel. intensity) 382 (100%), 509 (12%), 545 (19%), 586 (27%), 642 (7%) nm.
^{1}H NMR ($CDCl_3$) δ: 2.06-2.17 (m, 8H, NCH_3 and pyrrolidine-H), 2.27 (br s, 2H, pyrrolidine-H), 2.62-2.67 (m, 2H, pyrrolidine-H), 2.82-2.89 (m, 2H, pyrrolidine-H), 4.10 (br s, 2H, N*H*), 4.39-4.41 (m, 4H, reduced *β*-H), 7.09 (d, 2H, *β*-H, *J* 4.4 Hz), 7.55 (d, 2H, *β*-H, *J* 4.4 Hz).
^{19}F NMR ($CDCl_3$) δ: -185.13 to -184.96 (m, 2F, *m*-F), -184.35 to -184.17 (m, 2F, *m*-F), -183.98 to -183.85 (m, 2F, *m*-F), -182.64 to -182.50 (m, 2F, *m*-F), -176.05 to -175.68 (m, 3F, *p*-F), -174.31 (br s, 1F, *p*-F), -161.88 to -161.77 (m, 2F, *o*-F), -161.53 to -161.43 (m, 2F, *o*-F), -159.40 to -159.16 (m, 4F, *o*-F).
MS (FAB^+) 1089 $(M+H)^+$, 1088 $M^{+\bullet}$.

2.7.3: 1,3-Dipolar cycloaddition reactions of unsymmetric *meso*-tetraarylporphyrins with azomethine ylide 2.7

2.7.3.1: 5-Pentafluorophenyl-10,15,20-tris(4´-methoxyphenyl)porphyrin 2.10a[38]

A solution of pentafluorobenzaldehyde (1.15 mL, 9.3 mmol) and 4-methoxy benzaldehyde (2.63 mL, 21.6 mmol) in glacial acetic acid (210 mL) and nitrobenzene (150 mL) was heated at 120 ^oC. Pyrrole (2 mL, 28.8 mmol) was added dropwise within 15 minutes. The temperature was maintained at 120 ^oC for 45 minutes. The solution was cooled down to room temperature and kept overnight. The solvents were distilled under

vacuum. The residue was washed with light petroleum (3 × 20 mL) and separated by column chromatography (silica gel) using a gradient of chloroform/light petroleum as eluent. Porphyrin **2.10a** (0.46 g, 8% yield) was isolated from the statistical mixture of products.

UV-Vis ($CHCl_3$) λ_{max} (% rel. intensity) 417 (100%), 516 (9%), 553 (5%), 590 (4%), 648 (3%) nm.
^{1}H NMR ($CDCl_3$) δ: -2.74 (s, 2H, N*H*), 4.11 (s, 9H, 3 × OC*H*$_3$), 7.27-7.33 (m, 6H, Ph-H$_{meta}$), 8.13 (d, 6H, Ph-H$_{ortho}$, *J* 8.6 Hz), 8.75 (d, 2H, *β*-H, *J* 4.7 Hz), 8.87 and 8.88 (AB, 4H, *β*-H, *J* 4.9 Hz), 8.96 (d, 2H, *β*-H, *J* 4.7 Hz).
^{19}F NMR ($CDCl_3$) δ: -185.94 to -185.75 (m, 2F, *m*-F), -176.51 (t, 1F, *p*-F, *J* 21.2 Hz), -160.35 (dd, 2F, *o*-F, *J* 8.5 and 22.6 Hz).
MS (FAB$^+$) 795 $(M+H)^+$, 794 $M^{+\bullet}$.

2.7.3.2: 5-Pentafluorophenyl-10,15,20-triphenylporphyrin 2.10b

A solution of pentafluorobenzaldehyde (1.15 mL, 9.3 mmol) and benzaldehyde (2.20 mL, 21.6 mmol) in glacial acetic acid (210 mL) and nitrobenzene (150 mL) was heated at 120 ^{o}C. Pyrrole (2 mL, 28.8 mmol) was added dropwise within 15 minutes. The temperature was maintained at 120 ^{o}C for 45 minutes. The solution was cooled down to room temperature and kept overnight. The solvents were distilled under vacuum. The residue was washed with light petroleum (3 × 20 mL) and separated by column chromatography (silica gel) using a gradient of chloroform/light petroleum as eluent. Porphyrin **2.10b** (0.54 g, 11% yield) was isolated from the statistical mixture of products.

UV-Vis ($CHCl_3$) λ_{max} (% rel. intensity) 413 (100%), 513 (9%), 547 (4%), 587 (4%), 642 (2%) nm.
^{1}H NMR ($CDCl_3$) δ: -2.78 (s, 2H, N*H*), 7.74-7.81 (m, 9H, Ph-H$_{meta,para}$), 8.20-8.23 (m, 6H, Ph-H$_{ortho}$), 8.77 (d, 2H, *β*-H, *J* 4.8 Hz), 8.85 (AB, 4H, *β*-H, *J* 5.1 Hz), 8.94 (d, 2H, *β*-H, *J* 4.8 Hz).

^{19}F NMR ($CDCl_3$) δ: -185.85 to -185.66 (m, 2F, *m*-F), -176.51 (t, 1F, *p*-F, *J* 19.8 Hz), -160.34 (dd, 2F, *o*-F, *J* 8.5 and 22.6 Hz).
MS (FAB^+) 705 $(M+H)^+$, 704 $M^{+\bullet}$.

2.7.3.3: 5-(4′-Nitrophenyl)-10,15,20-triphenylporphyrin 2.10c[39]

A solution of 4-nitrobenzaldehyde (1.42 g, 9.3 mmol) and benzaldehyde (2.20 mL, 21.6 mmol) in glacial acetic acid (210 mL) and nitrobenzene (150 mL) was heated at 120 ^oC. Pyrrole (2 mL, 28.8 mmol) was added dropwise within 15 minutes. The temperature was maintained at 120 ^oC for 45 minutes. The solution was cooled down to room temperature and kept overnight. The solvents were distilled under vacuum. The residue was washed with light petroleum (3 × 20 mL) and separated by column chromatography (silica gel) using a gradient of chloroform/light petroleum as eluent. Porphyrin **2.10c** (0.28 g, 6% yield) was isolated from the statistical mixture of products.

UV-Vis ($CHCl_3$) λ_{max} (% rel. intensity) 419 (100%), 516 (7%), 552 (4%), 590 (3%), 646 (3%) nm.
^{1}H NMR ($CDCl_3$) δ: -2.79 (s, 2H, N*H*), 7.73-7.82 (m, 9H, Ph-$H_{meta,para}$), 8.20-8.23 (m, 6H, Ph-H_{ortho}), 8.41 (d, 2H, 4-$NO_2C_6H_4$-H_{ortho}, *J* 8.7 Hz), 8.65 (d, 2H, 4-$NO_2C_6H_4$-H_{meta}, *J* 8.7 Hz), 8.75 (d, 2H, *β*-H, *J* 4.9 Hz), 8.86 (AB, 2H, *β*-H, *J* 4.8 Hz), 8.90 (d, 2H, *β*-H, *J* 4.9 Hz).
MS (FAB^+) 660 $(M+H)^+$, 659 $M^{+\bullet}$.

2.7.3.4: 1,3-Dipolar cycloaddition reaction of porphyrin 2.10a with azomethine ylide 2.7

A solution of porphyrin **2.10a** (20 mg), *N*-methylglycine (4 mg, 2 equiv.), and paraformaldehyde (4 mg, 5 equiv.) in toluene (5 mL) was refluxed for 8 hours under a nitrogen atmosphere. The reaction was monitored by TLC. Further portions of *N*-

methylglycine (4 mg) and paraformaldehyde (4 mg) were then added and refluxed for another 8 hours. The total reaction time was 56 hours (8 hours × 7). The solvent was evaporated and the residue was separated by column chromatography (silica gel) using a gradient of $CHCl_3$-light petroleum. Three fractions were isolated: the first one was the unchanged starting porphyrin **2.10a** (9.5 mg, 48%) and the next two fractions correspond to two mono-adducts, **2.11a** (6.4 mg, 30% yield) and **2.12a** (2.0 mg, 9% yield). The two adducts were purified by preparative TLC.

2.11a:

mp > 300 ˚C.

UV-Vis ($CHCl_3$) λ_{max} (log ε) 418 (5.33), 517 (4.24), 545 (4.24), 594 (3.98), 647 (4.60) nm.

^{1}H NMR ($CDCl_3$) δ: -1.54 (s, 1H, N*H*), -1.42 (s, 1H, N*H*), 2.14 (s, 3H, NCH_3), 2.35-2.46 (m, 2H, pyrrolidine-H), 3.00 (t, 1H, pyrrolidine-H, *J* 8.5 Hz), 3.08 (t, 1H, pyrrolidine-H, *J* 8.5 Hz), 4.04 (s, 3H, OCH_3), 4.056 (s, 3H, OCH_3), 4.062 (s, 3H, OCH_3), 5.11 (q, 1H, reduced *β*-H, *J* 8.5 Hz), 5.40 (q, 1H, reduced *β*-H, *J* 8.5 Hz), 7.18-7.24 (m, 6H, Ph-H$_{meta}$), 7.84 (d, 2H, Ph-H$_{ortho}$, *J* 8.6 Hz), 7.98-8.06 (m, 4H, Ph-H$_{ortho}$), 8.17 (d, 1H, *β*-H, *J* 4.9 Hz), 8.26 (d, 1H, *β*-H, *J* 4.9 Hz), 8.44 and 8.45 (AB, 2H, *β*-H, *J* 4.6 Hz), 8.62 (d, 1H, *β*-H, *J* 4.9 Hz), 8.69 (d, 1H, *β*-H, *J* 4.9 Hz).

^{19}F NMR ($CDCl_3$) δ: -185.16 to -185.00 (m, 1F, *m*-F), -184.81 to -184.67 (m, 1F, *m*-F), -176.68 (t, 1F, *p*-F, *J* 19.8 Hz), -161.26 (dd, 1F, *o*-F, *J* 7.1 and 24.0 Hz), -159.15 (dd, 1F, *o*-F, *J* 7.1 and 24.0 Hz).

MS (FAB$^+$) 852 $(M+H)^+$, 851 $M^{+\bullet}$.

Anal. Calcd for $C_{50}H_{38}F_5N_5O_3$: C, 70.50; H, 4.50; N, 8.22; Found: C, 70.64; H, 4.51; N, 8.13.

2.12a:

mp > 300 ˚C.

UV-Vis $CHCl_3$) λ_{max} (log ε) 422 (5.40), 518 (4.33), 548 (4.20), 598 (4.04), 652 (4.63) nm.

^{1}H NMR ($CDCl_3$) δ: -1.99 (s, 1H, N*H*), -1.93 (s, 1H, N*H*), 2.07 (s, 3H, NCH_3), 2.29-2.36 (m, 2H, pyrrolidine-H), 2.96-3.01 (m, 2H, pyrrolidine-H), 4.048 (s, 3H, OCH_3), 4.051 (s, 3H, OCH_3), 4.07 (s, 3H, OCH_3), 5.33-5.43 (m, 2H, reduced *β*-H), 7.19-7.25 (m, 6H, Ph-H$_{meta}$), 7.83-7.89 (m, 4H, Ph-H$_{ortho}$), 8.00 (d, 1H, Ph-H$_{ortho}$, *J* 7.8 Hz), 8.06 (d, 1H, Ph-H$_{ortho}$,

J 7.8 Hz), 8.32 (d, 1H, *β*-H, *J* 4.5 Hz), 8.39 (d, 1H, *β*-H, *J* 4.5 Hz), 8.42 (d, 1H, *β*-H, *J* 5.0 Hz), 8.55 (d, 1H, *β*-H, *J* 5.0 Hz), 8.58 (d, 1H, *β*-H, *J* 4.7 Hz), 8.67 (d, 1H, *β*-H, *J* 4.7 Hz).
^{19}F NMR ($CDCl_3$) δ: -186.16 to -185.87 (m, 2F, *m*-F), -176.96 (t, 1F, *p*-F, *J* 21.2 Hz), -160.84 (dd, 1F, *o*-F, *J* 8.5 and 25.4 Hz), -160.63 (dd, 1F, *o*-F, *J* 8.5 and 22.6 Hz).
MS (FAB^+) 852 $(M+H)^+$, 851 $M^{+\bullet}$.
HRMS (ESI) Calcd for $C_{50}H_{39}F_5N_5O_3$ $(M+H)^+$ 852.2968; Found. 852.2959.
Anal. Calcd for $C_{50}H_{38}F_5N_5O_3$: C, 70.50; H, 4.50; N, 8.22; Found: C, 70.00; H, 4.45; N, 8.13.

2.7.3.5: 1,3-Dipolar cycloaddition reaction of porphyrin 2.10b with azomethine ylide 2.7

A solution of porphyrin **2.10b** (20 mg), *N*-methylglycine (5 mg, 2 equiv.), and paraformaldehyde (5 mg, 5 equiv.) in toluene (5 mL) was refluxed for 8 hours under a nitrogen atmosphere. The reaction was monitored by TLC. Further portions of *N*-methylglycine (5 mg) and paraformaldehyde (5 mg) were then added and refluxed for another 8 hours. The total reaction time was 56 hours (8 hours × 7). The solvent was evaporated and the residue was separated by column chromatography (silica gel) using a gradient of $CHCl_3$-light petroleum. Three fractions were isolated: the first one was the unchanged starting porphyrin **2.10b** (16.2 mg, 81%) and the next two fractions correspond to two mono-adducts, **2.11b** (1.9 mg, 9% yield) and **2.12b** (0.9 mg, 4% yield). The two adducts were purified by preparative TLC.

2.11b:
mp > 300 ˚C.
UV-Vis ($CHCl_3$) λ_{max} (log ε) 366 (4.59), 414 (5.27), 513 (4.25), 540 (4.18), 594 (3.95), 647 (4.59) nm.
^{1}H NMR ($CDCl_3$) δ: -1.58 (s, 1H, N*H*), -1.48 (s, 1H, N*H*), 2.14 (s, 3H, NCH_3), 2.39-2.48 (m, 2H, pyrrolidine-H), 2.94 (t, 1H, pyrrolidine-H, *J* 8.5 Hz), 3.08 (t, 1H, pyrrolidine-H, *J* 8.5 Hz), 5.13 (q, 1H, reduced *β*-H, *J* 8.5 Hz), 5.40 (q, 1H, reduced *β*-H, *J* 8.5 Hz), 7.66-

7.74 (m, 9H, Ph-$H_{meta,para}$), 7.93-7.96 (m, 2H, Ph-H_{ortho}), 8.05-8.14 (m, 4H, Ph-H_{ortho}), 8.18 (d, 1H, *β*-H, *J* 4.7 Hz), 8.24 (d, 1H, *β*-H, *J* 4.7 Hz), 8.41 and 8.42 (AB, 2H, *β*-H, *J* 4.6 Hz), 8.59 (d, 1H, *β*-H, *J* 4.8 Hz), 8.67 (d, 1H, *β*-H, *J* 4.8 Hz).

^{19}F NMR ($CDCl_3$) -185.11 to -184.92 (m, 1F, *m*-F), -184.81 to -184.58 (m, 1F, *m*-F), -176.53 (t, 1H, *p*-F, *J* 19.8 Hz), -161.25 (dd, 1H, *o*-F, *J* 6.8 and 24.0 Hz), -159.13 (dd, 1H, *o*-F, *J* 5.1 and 23.7 Hz).

MS (FAB^+) 762 $(M+H)^+$, 761 $M^{+\bullet}$.

Anal. Calcd for $C_{47}H_{32}F_5N_5 \cdot 3H_2O$: C, 69.19; H, 4.69; N, 8.58; Found: C, 69.25; H, 4.74; N, 8.47.

2.12b:

mp > 300 ˚C.

UV-Vis ($CHCl_3$) λ_{max} (log ε) 416 (5.22), 515 (4.23), 544 (4.02), 597 (3.87), 651 (4.55) nm.

^{1}H NMR ($CDCl_3$) δ: -1.99 (s, 1H, N*H*), -1.94 (s, 1H, N*H*), 2.08 (s, 3H, NCH_3), 2.29-2.43 (m, 2H, pyrrolidine-H), 2.91-2.99 (m, 2H, pyrrolidine-H), 5.36-5.44 (m, 2H, reduced *β*-H), 7.69-7.73 (m, 9H, Ph-$H_{meta,para}$), 7.94-8.00 (m, 4H, Ph-H_{ortho}), 8.08-8.10 (m, 1H, Ph-H_{ortho}), 8.14-8.16 (m, 1H, Ph-H_{ortho}), 8.30 (d, 1H, *β*-H, *J* 4.8 Hz), 8.40 (d, 2H, *β*-H, *J* 4.6 Hz), 8.56 (d, 2H, *β*-H, *J* 4.6 Hz), 8.64 (d, 1H, *β*-H, *J* 4.8 Hz).

^{19}F NMR ($CDCl_3$) δ: -186.08 to -185.81 (m, 2F, *m*-F), -176.79 (t, 1F, *p*-F, *J* 21.2 Hz), -160.84 (dd, 1F, *o*-F, *J* 7.1 and 24.0 Hz), -160.62 (dd, 1F, *o*-F, *J* 8.5 and 22.6 Hz).

MS (FAB^+) 762 $(M+H)^+$, 761 $M^{+\bullet}$.

Anal. Calcd for $C_{47}H_{32}F_5N_5 \cdot 3H_2O$: C, 69.19; H, 4.69; N, 8.58; Found: C, 69.14; H, 4.76; N, 8.37.

2.7.3.6: 1,3-Dipolar cycloaddition reaction of porphyrin 2.10c with azomethine ylide 2.7

A solution of porphyrin **2.10c** (20 mg), *N*-methylglycine (5 mg, 2 equiv.) and paraformaldehyde (5 mg, 5 equiv.) in toluene (5 mL) was refluxed for 8 hours under a nitrogen atmosphere. The reaction monitored by TLC. Further portions of *N*-methylglycine

(5 mg) and paraformaldehyde (5 mg) were then added and refluxed for another 8 hours. The total reaction time was 56 hours (8 hours × 7). The solvent was evaporated and the residue was separated by column chromatography (silica gel) using a gradient of $CHCl_3$-light petroleum. Three fractions were isolated: the first one was the unchanged starting porphyrin **2.10c** (16.9 mg, 85%) and the next two fractions correspond to two mono-adducts, **2.11c** (1.3 mg, 6% yield) and **2.12c** (1.1 mg, 5% yield). The two adducts were purified by preparative TLC.

2.11c:

mp > 300 ˚C.

UV-Vis($CHCl_3$) λ_{max} (log ε) 368 (4.55), 419 (5.25), 517 (4.24), 545 (4.20), 595 (3.93), 648 (4.53) nm.

^{1}H NMR ($CDCl_3$) δ: -1.67 (s, 1H, N*H*), -1.64 (s, 1H, N*H*), 2.05 (s, 3H, NCH_3), 2.33-2.42 (m, 2H, pyrrolidine-H), 2.84-2.90 (m, 2H, pyrrolidine-H), 5.30-5.36 (m, 2H, reduced *β*-H), 7.65-7.72 (m, 9H, Ph-$H_{meta,para}$), 7.92-7.98 (m, 2H, Ph-H_{ortho}), 8.07-8.21 (m, 7H, Ph-H_{ortho}, *β*-H and 4-$NO_2C_6H_4$-H_{ortho}), 8.26 (d, 1H, *β*-H, *J* 5.0 Hz), 8.436 and 8.444 (AB, 2H, *β*-H, *J* 4.6 Hz), 8.55-8.63 (m, 4H, 4-$NO_2C_6H_4$-H_{meta} and *β*-H).

MS (FAB^+) 717 $(M+H)^+$, 716 $M^{+\bullet}$.

HRMS (ESI) Calcd for $C_{47}H_{37}N_6O_2$ $(M+H)^+$ 717.2978; Found 717.2951.

Anal. Calcd for $C_{47}H_{36}N_6O_2 \cdot 1.5H_2O$: C, 75.89; H, 5.28; N, 11.30; Found: C, 75.45; H, 5.45; N, 11.69.

2.12c:

mp > 300 ˚C.

UV-Vis ($CHCl_3$) λ_{max} (log ε) 420 (5.27), 519 (4.30), 547 (4.19), 596 (3.99), 649 (4.53) nm.

^{1}H NMR ($CDCl_3$) δ: -1.83 (s, 2H, N*H*), 2.05 (s, 3H, NCH_3), 2.36-2.41 (m, 2H, pyrrolidine-H), 2.87-2.90 (m, 2H, pyrrolidine-H), 5.32-5.42 (m, 2H, reduced *β*-H), 7.66-7.74 (m, 9H, Ph-$H_{meta,para}$), 7.93-7.98 (m, 4H, Ph-H_{ortho}), 8.08-8.10 (m, 1H, Ph-H_{ortho}), 8.13-8.14 (m, 1H, Ph-H_{ortho}), 8.25-8.35 (m, 5H, 4-$NO_2C_6H_4$-H_{ortho} and *β*-H), 8.49-8.51 (m, 2H, *β*-H), 8.57-8.60 (m, 2H, 4-$NO_2C_6H_4$-H_{meta}), 8.63 (d, 1H, *β*-H, *J* 4.9 Hz).

MS (FAB^+) 717 $(M+H)^+$, 716 $M^{+\bullet}$.

HRMS (FAB^+) Calcd for $C_{47}H_{37}N_6O_2$ $(M+H)^+$ 717.2978; Found 717.2999.

Anal. Calcd for $C_{47}H_{36}N_6O_2 \cdot 0.5H_2O$: C, 77.77; H, 5.14; N, 11.58; Found: C, 77.57; H, 5.65; N, 11.51.

2.7.3.7: 1,3-Dipolar cycloaddition reaction of porphyrin 2.10b with azomethine ylide $^-CH_2{}^+N(CH_2)Bn$

A solution of porphyrin **2.10b** (20 mg), *N*-benzylglycine (11 mg, 2 equiv.), paraformaldehyde (5 mg, 5 equiv.) and potassium carbonate (16 mg, 4 equiv.) in toluene (5 mL) was refluxed for 8 hours under a nitrogen atmosphere. the reaction was monitored by TLC. Further portions of *N*-benzylglycine (11 mg), paraformaldehyde (5 mg) and potassium carbonate (16 mg) were then added and refluxed for another 8 hours. The total reaction time was 56 hours (8 hours × 7). The solvent was evaporated and the residue was separated by column chromatography (silica gel) using a gradient of $CHCl_3$-light petroleum. Three fractions were isolated: the first one was the unchanged starting porphyrin **2.10b** (16.6 mg, 83%) and the next two fractions correspond to two mono-adducts, **2.11d** (2.3 mg, 10% yield) and **2.12d** (0.9 mg, 4% yield). The two adducts were purified by preparative TLC.

2.11d:

mp > 300 ˚C.

UV-Vis ($CHCl_3$) λ_{max} (log ε) 365 (4.60), 415 (5.30), 513 (4.26), 539 (4.18), 594 (3.94), 646 (4.61) nm.

^{1}H NMR ($CDCl_3$) δ: -1.58 (s, 1H, N*H*), -1.49 (s, 1H, N*H*), 2.41-2.51 (m, 2H, pyrrolidine-H), 3.01 (t, 2H, pyrrolidine-H, *J* 8.7 Hz), 3.26 (d, 1H, C*H*$_2$Ph, *J* 12.4 Hz), 3.45 (d, 1H, C*H*$_2$Ph, *J* 12.4 Hz), 5.06 (q, 1H, reduced *β*-H, *J* 8.7 Hz), 5.34 (q, 1H, reduced *β*-H, *J* 8.7 Hz), 7.05-7.08 (m, 2H, CH_2Ph-H$_{ortho}$), 7.23-7.25 (m, 3H, CH_2Ph-H$_{meta,para}$), 7.60-7.76 (m, 9H, Ph-H$_{meta,para}$), 7.86-7.89 (m, 1H, Ph-H$_{ortho}$), 7.92-7.95 (m, 1H, Ph-H$_{ortho}$), 8.06-8.13 (m, 4H, Ph-H$_{ortho}$), 8.19 (d, 1H, *β*-H, *J* 4.8 Hz), 8.23 (d, 1H, *β*-H, *J* 4.9 Hz), 8.42 and 8.43 (AB, 2H, *β*-H, *J* 4.6 Hz), 8.60 (d, 1H, *β*-H, *J* 4.9 Hz) 8.68 (d, 1H, *β*-H, *J* 4.8 Hz).

^{19}F NMR ($CDCl_3$) δ: -185.56 to -185.40 (m, 1F, *m*-F), -184.69 to -184.50 (m, 1F, *m*-F), -176.65 (t, 1F, *p*-F, *J* 19.8 Hz), -161.40 (dd, 1F, *o*-F, *J* 8.5 and 25.4 Hz), -159.11 (dd, 1F, *o*-F, *J* 7.1 and 24.0 Hz).

MS (FAB^+) 838 $(M+H)^+$, 837 $M^{+\bullet}$.

Anal. Calcd for $C_{53}H_{36}F_5N_5 \cdot H_2O$: C, 74.37; H, 4.48; N, 8.18; Found: C, 74.17; H, 4.84; N, 8.57.

2.12d:

mp > 300 ˚C.

UV-Vis ($CHCl_3$) λ_{max} (log ε) 419 (5.35), 515 (4.29), 543 (4.09), 597 (3.96), 650 (4.60) nm.

^{1}H NMR ($CDCl_3$) δ: -1.99 (s, 1H, N*H*), -1.94 (s, 1H, N*H*), 2.35-2.44 (m, 2H, pyrrolidine-H), 2.91-2.96 (m, 2H, pyrrolidine-H), 3.29 (s, 2H, CH_2Ph), 5.28-5.36 (m, 2H, reduced *β*-H), 6.98-7.01 (m, 2H, CH_2Ph-H_{ortho}), 7.17-7.23 (m, 3H, CH_2Ph-$H_{meta,para}$), 7.59-7.79 (m, 9H, Ph-$H_{mata,para}$), 7.86-7.92 (m, 4H, Ph-H_{ortho}), 8.09-8.11 (m, 1H, Ph-H_{ortho}), 8.14-8.116 (m, 1H, Ph-H_{ortho}), 8.29 (d, 1H, *β*-H, *J* 4.7 Hz), 8.38-8.41 (m, 2H, *β*-H), 8.56 (d, 2H, *β*-H, *J* 4.6 Hz), 8.64 (d, 1H, *β*-H, *J* 4.7 Hz).

^{19}F NMR ($CDCl_3$) δ: -186.08 to -185.45 (m, 2F, *m*-F), -176.81 (t, 1F, *p*-F, *J* 19.8 Hz), -160.83 (dd, 1F, *o*-F, *J* 8.5 and 25.4 Hz), -160.63 (dd, 1F, *o*-F, *J* 8.5 and 25.4 Hz).

MS (FAB^+) 838 $(M+H)^+$, 837 $M^{+\bullet}$.

HRMS (FAB^+) Calcd for $C_{53}H_{37}F_5N_5$ $(M+H)^+$ 838.2969; Found 838.2965.

2.7.4: Intramolecular 1,3-dipolar cycloaddition reactions of *meso*-(*o*-formylphenyl)porphyrins

2.7.4.1: 2-(1′,3′-Dithiacyclohexan-2′-yl)benzaldehyde 2.13[25]

Samples of *o*-phthalaldehyde (0.67 g, 5 mmol) and propane-1,3-dithiol (0.50 mL, 5 mmol) were placed in a 50 mL flask containing dry CH_2Cl_2 (20 mL). Boron trifluoride etherate (0.12 mL) was added and the mixture was stirred overnight at room temperature.

The mixture was extracted with 5% NaOH (10 mL), washed with water (3 × 20 mL), and dried with Na_2SO_4. The solution was concentrated, it was left to crystallize and the white solid was filtered to afford **2.13** (0.73 g, 65% yield).

mp 83-86 ^oC.

^1H NMR ($CDCl_3$) δ: 1.87-2.00 (m, 1H, H_d), 2.16-2.24 (m, 1H, H_c), 2.88-2.96 (m, 2H, H_b), 3.09-3.19 (m, 2H, H_a), 6.24 (s, 1H, C*H*), 7.47 (dt, 1H, Ph-H, *J* 1.1 and 7.6 Hz), 7.58 (dt, 1H, Ph-H, *J* 1.4 and 7.6 Hz), 7.76 (dd, 1H, Ph-H, *J* 1.1 and 7.6 Hz), 7.83 (dd, 1H, Ph-H, *J* 1.4 and 7.6 Hz), 10.39 (s, 1H, C*H*O).

MS (EI) 224 $M^{+\bullet}$.

2.7.4.2: 5-[2´-(1´´,3´´-Dithiacyclohexan-2´´-yl)phenyl]-10,15,20-tris(3´,4´,5´-trifluorophenyl)porphyrin 2.14a

Boron trifluoride etherate (0.05 mL) was added to a solution of 3,4,5-trifluorobenzaldehyde (0.34 mL, 3 mmol), dithianyl-protected *o*-phthalaldehyde **2.13** (0.29 g, 1.3 mmol) and pyrrole (0.28 mL, 4 mmol) in CH_2Cl_2 (125 mL). The mixture was stirred at room temperature under nitrogen and protected from light. The condensation gave a mixture of porphyrinogens which after 1 hour were oxidized with DDQ (0.72 g, 3.2 mmol). Stirring was continued at room temperature for 3 hours. Triethylamine (TEA, 0.5 mL) was added and the solvent was evaporated under vacuum. The residue was separated by column chromatography (silica gel) using a gradient of chloroform/light petroleum as eluent. The unsymmetrical *meso*-tetraarylporphyrin **2.14a** (0.14 g, 16% yield) was isolated from the statistical mixture of products.

mp > 300 ˚C.

UV-Vis ($CHCl_3$) λ_{max} 414 (100%), 512 (11%), 545 (3%), 587 (4%), 643 (2%) nm.

^1H NMR ($CDCl_3$) δ: -2.87 (s, 2H, N*H*), 1.55-1.69 (m, 2H, H_c and H_d), 1.84-1.94 (m, 2H, H_b), 2.33-2.38 (m, 2H, H_a), 4.76 (s, 1H, C*H*), 7.57 (dt, 1H, Ph-H, *J* 1.2 and 7.7 Hz), 7.77-

7.98 (m, 8H, Ph-H), 8.21 (dd, 1H, Ph-H, *J* 0.8 and 7.7 Hz), 8.87 (AB, 4H, *β*-H, *J* 4.8 Hz), 8.95 (AB, 4H, *β*-H, *J* 4.7 Hz).
MS (FAB^+) 895 $(M+H)^+$, 894 $M^{+\bullet}$.

2.7.4.3: 5-[2´-(1´´,3´´-Dithiacyclohexan-2´´-yl)phenyl]-10,15,20-tris(2´,3´,6´-trifluorophenyl)porphyrin 2.14b

Boron trifluoride etherate (0.05 mL) was added to a solution of 2,3,6-trifluorobenzaldehyde (0.34 mL, 3 mmol), dithianyl-protected *o*-phthalaldehyde **2.13** (0.29 g, 1.3 mmol) and pyrrole (0.28 mL, 4 mmol) in CH_2Cl_2 (125 mL). The mixture was stirred at room temperature under nitrogen and protected from light. The condensation gave a mixture of porphyrinogens which after 1 hour were oxidized with DDQ (0.72 g, 3.2 mmol). Stirring was continued at room temperature for 3 hours. TEA (0.5 mL) was added and the solvent was evaporated under vacuum. The residue was separated by column chromatography (silica gel) using a gradient of chloroform/light petroleum as eluent. The unsymmetrical *meso*-tetraarylporphyrin **2.14b** (38 mg, 4% yield) was isolated from the statistical mixture of products.

mp > 300 ˚C.
UV-Vis ($CHCl_3$) λ_{max} (% rel. intensity) 413 (100%), 509 (9%), 539 (2%), 584 (4%), 639 (1%) nm.
^{1}H NMR ($CDCl_3$) δ: -2.77 (s, 2H, N*H*), 1.53-1.63 (m, 2H, H_c and H_d), 1.84-1.92 (m, 2H, H_b), 2.30-2.36 (m, 2H, H_a), 4.71 (s, 1H, C*H*), 7.23-7.34 (m, 3H, Ph-H), 7.58-7.66 (m, 4H, Ph-H), 7.85 (dt, 1H, Ph-H, *J* 1.0 and 7.7 Hz), 7.96-7.99 (m, 1H, Ph-H), 8.20 (dd, 1H, Ph-H, *J* 0.5 and 7.7 Hz), 8.83 (AB, 4H, *β*-H, *J* 5.3 Hz), 8.91 (AB, 4H, *β*-H, *J* 5.0 Hz).
MS (FAB^+) 895 $(M+H)^+$, 894 $M^{+\bullet}$.

2.7.4.4: 5-[2´-(1´´,3´´-Dithiacyclohexan-2´´-yl)phenyl]-10,15,20-tris(pentafluorophenyl)porphyrin 2.14c

Boron trifluoride etherate (0.10 mL) was added to a solution of pentafluorobenzaldehyde (0.74 mL, 6 mmol), dithianyl-protected *o*-phthalaldehyde **2.13** (0.58 g, 2.6 mmol) and pyrrole (0.56 mL, 8 mmol) in CH_2Cl_2 (250 mL). The mixture was stirred at room temperature under nitrogen and protected from light. The condensation gave a mixture of porphyrinogens which after 1 hour were oxidized with DDQ (1.44 g, 6.4 mmol). Stirring was continued at room temperature for 3 hours. TEA (1.0 mL) was added and the solvent was evaporated under vacuum. The residue was separated by column chromatography (silica gel) using a gradient of chloroform/light petroleum as eluent. The unsymmetrical *meso*-tetraarylporphyrin **2.14c** (85 mg, 4% yield) was isolated from the statistical mixture of products.

mp > 300 ˚C.

UV-Vis ($CHCl_3$) λ_{max} (% rel. intensity) 414 (100%), 509 (10%), 539 (3%), 584 (4%), 638 (2%) nm.

^{1}H NMR ($CDCl_3$) δ: -2.81 (s, 2H, N*H*), 1.57-1.64 (m, 2H, H_c and H_d), 1.83-1.92 (m, 2H, H_b), 2.29-2.37 (m, 2H, H_a), 4.68 (s, 1H, C*H*), 7.62 (dt, 1H, Ph-H, *J* 0.9 and 7.5 Hz), 7.87 (dt, 1H, Ph-H, *J* 0.9 and 7.5 Hz), 7.98 (dd, 1H, Ph-H, *J* 0.9 and 7.5 Hz), 8.23 (br d, 1H, Ph-H, *J* 7.5 Hz), 8.87 (d, 2H, *β*-H, *J* 4.9 Hz), 8.91 (d, 2H, *β*-H, *J* 4.9 Hz), 8.95 (AB, 4H, *β*-H, *J* 4.9 Hz).

MS (FAB^+) 1003 $(M+H)^+$, 1002 $M^{+\bullet}$.

2.7.4.5: 5-(2´-Formylphenyl)-10,15,20-tris(3´,4´,5´-trifluorophenyl)porphyrin 2.15a

Boron trifluoride etherate (0.1 mL) was added to a solution of porphyrin **2.14a** (20 mg), DDQ (25 mg, 5 equiv.) in CH_2Cl_2 (5 mL). The mixture was stirred at room temperature overnight in air. The solvent was evaporated under vacuum and porphyrin **2.15a** (15.4 mg,

86% yield) was separated by column chromatography (silica gel) using chloroform/light petroleum (1:1) as eluent.

mp > 300 ˚C.
UV-Vis ($CHCl_3$) λ_{max} (% rel. intensity) 414 (100%), 512 (10%), 546 (3%), 588 (4%), 644 (2%) nm.
^{1}H NMR ($CDCl_3$) δ: -2.88 (s, 2H, N*H*), 7.82-8.00 (m, 8H, Ph-H), 8.22-8.25 (m, 1H, Ph-H), 8.41-8.44 (m, 1H, Ph-H), 8.83 (d, 2H, *β*-H, *J* 4.8 Hz), 8.85 (d, 2H, *β*-H, *J* 4.8 Hz), 8.89 (AB, 4H, *β*-H, *J* 4.8 Hz), 9.46 (s, 1H, C*H*O).
MS (FAB^+) 805 $(M+H)^+$, 804 $M^{+\bullet}$.

2.7.4.6: 5-(2´-Formylphenyl)-10,15,20-tris(2´,3´,6´-trifluorophenyl)porphyrin 2.15b

Boron trifluoride etherate (0.1 mL) was added to a solution of porphyrin **2.14b** (20 mg), DDQ (25 mg, 5 equiv.) in CH_2Cl_2 (5 mL). The mixture was stirred at room temperature overnight in air. The solvent was evaporated under vacuum and porphyrin **2.15b** (15.5 mg, 86% yield) was separated by column chromatography (silica gel) using chloroform/light petroleum (1:1) as eluent.

mp > 300 ˚C.
UV-Vis ($CHCl_3$) λ_{max} (% rel. intensity) 414 (100%), 510 (10%), 541 (2%), 585 (4%), 641 (1%) nm.
^{1}H NMR ($CDCl_3$) δ: -2.70 (s, 2H, N*H*), 7.29-7.30 (m, 3H, Ph-H), 7.56-7.66 (m, 3H, Ph-H), 7.84-7.95 (m, 2H, Ph-H), 8.19-8.22 (m, 1H, Ph-H), 8.41 (d, 1H, Ph-H, *J* 7.6 Hz), 8.73 (d, 2H, *β*-H, *J* 4.7 Hz), 8.85 (d, 2H, *β*-H, *J* 4.7 Hz), 8.91 (AB, 4H, *β*-H, *J* 4.8 Hz), 9.51 (s, 1H, C*H*O).
MS (FAB^+) 805 $(M+H)^+$, 804 $M^{+\bullet}$.

2.7.4.7: 5-(2´-Formylphenyl)-10,15,20-tris(pentafluorophenyl)porphyrin 2.15c

Boron trifluoride etherate (0.4 mL) was added to a solution of porphyrin **2.14c** (77 mg), DDQ (87 mg, 5 equiv.) in CH_2Cl_2 (20 mL). The mixture was stirred at room temperature overnight in air. The solvent was evaporated under vacuum and porphyrin **2.15c** (42.0 mg, 60% yield) was separated by column chromatography (silica gel) using chloroform/light petroleum (1:1) as eluent.

mp > 300 ˚C.
UV-Vis ($CHCl_3$) λ_{max} (% rel. intensity) 411 (100%), 508 (12%), 539 (2%), 584 (4%), 639 (2%) nm.
^{1}H NMR ($CDCl_3$) δ: -2.78 (s, 2H, N*H*), 7.96 (dt, 1H, Ph-H, *J* 1.3 and 7.2 Hz), 8.02 (dd, 1H, Ph-H, *J* 1.3 and 7.2 Hz), 8.24 (dd, 1H, Ph-H, *J* 1.3 and 7.2 Hz), 8.43-8.46 (m, 1H, Ph-H), 8.77-8.92 (m, 8H, *β*-H), 9.49 (s, 1H, C*H*O).
MS (FAB^+) 913 $(M+H)^+$, 912 $M^{+\bullet}$.

2.7.4.8: Intramolecular cycloaddition reaction of porphyrin 2.15a

A solution of porphyrin **2.15a** (20 mg) and *N*-methylglycine (11 mg, 5 equiv.) in toluene (5 mL) was refluxed for 6 hours under a nitrogen atmosphere. TLC of the reaction mixture revealed complicated results. The solvent was evaporated and the residue was separated by column chromatography (silica gel) using a gradient of chloroform/light petroleum as eluent. The starting porphyrin **2.15a** (13.9 mg, 70%) was recovered and then the expected chlorin **2.16a** (0.4 mg, 2% yield) was isolated.

UV-Vis ($CHCl_3$) λ_{max} (% rel. intensity) 428 (100%), 534 (7%), 569 (12%), 615 (5%), 671 (18%) nm.
MS (FAB^+) 832 $(M+H)^+$, 831 $M^{+\bullet}$.

2.7.4.9: Intramolecular cycloaddition reaction of porphyrin 2.15c

A solution of porphyrin **2.15c** (20 mg) and *N*-methylglycine (10 mg, 5 equiv.) in toluene (5 mL) was refluxed for 6 hours under a nitrogen atmosphere. TLC of the reaction mixture revealed complicated results. The solvent was evaporated and the residue was separated by column chromatography (silica gel) using a gradient of chloroform/light petroleum as eluent. The methylene-bridged porphyrin **2.17** (3.0 mg, 10% yield) was isolated in the first fraction, the second fraction − the starting porphyrin **2.15c** (3.6 mg, 18%) was recovered and the third fraction − the expected chlorin **2.16c** (1.3 mg, 6% yield) was isolated.

2.16c:

UV-Vis ($CHCl_3$) λ_{max} (% rel. intensity) 425 (100%), 528 (7%), 562 (9%), 618 (4%), 675 (21%) nm.

^{1}H NMR ($CDCl_3$) δ: -1.01 (s, 1H, N*H*), -0.66 (s, 1H, N*H*), 2.42 (s, 3H, NCH_3), 2.87 (t, 1H, pyrrolidine-H, *J* 9.8 Hz), 3.18 (d, 1H, pyrrolidine-H, *J* 9.8 Hz), 3.98 (d, 1H, pyrrolidine-H, *J* 4.6 Hz), 4.75 (dd, 1H, reduced *β*-H, *J* 4.6 and 7.7 Hz), 4.92-4.98 (m, 1H, reduced *β*-H), 7.64 (dt, 1H, Ph-H, *J* 1.0 and 7.5 Hz), 7.77 (dd, 1H, Ph-H, *J* 1.2 and 7.5 Hz), 7.86 (dt, 1H, Ph-H, *J* 1.2 and 7.5 Hz), 8.21 (d, 1H, *β*-H, *J* 4.9 Hz), 8.36 (d, 1H, *β*-H, *J* 4.6 Hz), 8.40 (d, 1H, *β*-H, *J* 4.6 Hz), 8.54-8.62 (m, 3H, Ph-H and *β*-H), 9.10 (d, 1H, *β*-H, *J* 4.9 Hz).

MS (FAB$^+$) 940 $(M+H)^+$, 939 $M^{+\bullet}$.

2.17:

UV-Vis ($CHCl_3$) λ_{max} (% rel. intensity) 436 (100%), 546 (11%), 583 (12%), 635 (10%), 695 (25%) nm.

^{1}H NMR ($CDCl_3$) δ: 5.16 (s, 2H, CH_2), 7.80 (t, 1H, Ph-H, *J* 7.7 Hz), 7.96 (dt, 1H; Ph-H, *J* 1.2 and 7.7 Hz), 8.13 (d, 1H, *β*-H, *J* 4.6 Hz), 8.19 (d, 1H, *β*-H, *J* 5.2 Hz), 8.29-8.41 (m, 4H, *β*-H and Ph-H), 8.55 (s, 1H, *β*-H), 9.15 (d, 1H, *β*-H, *J* 4.6 Hz), 9.38 (d, 1H, Ph-H, *J* 7.7 Hz).

MS (FAB$^+$) 897 $(M+H)^+$, 896 $M^{+\bullet}$.

2.7.4.10: Attempt to synthesize 2.18a from one pot reaction of porphyrin 2.15a

A solution of porphyrin **2.15a** (20 mg), *N*-methylglycine (11 mg, 5 equiv.) and DDQ (28 mg, 5 equiv.) in toluene (6 mL) was refluxed for 6 hours under a nitrogen atmosphere. TLC of the reaction mixture revealed that a new green product as only one spot. The solvent was evaporated, the residue was separated by column chromatography (silica gel) using a mixture of $CHCl_3$-light petroleum (1:1), the green compound **2.19a** (7.1 mg, 36%) was isolated.

mp > 300 ˚C.
UV-Vis ($CHCl_3$) λ_{max} (% rel. intensity) 378 (32%), 460 (100%), 531 (4%), 572 (5%), 628 (8%), 730 (7%) nm.
^{1}H NMR ($CDCl_3$) δ: -1.01 (s, 2H, N*H*), 7.43 (t, 1H, Ph-H, *J* 7.6 Hz), 7.67-7.79 (m, 7H, Ph-H), 8.16 (d, 1H, Ph-H, *J* 7.6 Hz), 8.37 (d, 1H, Ph-H, *J* 7.6 Hz), 8.55 (d, 1H, *β*-H, *J* 4.9 Hz), 8.59-8.67 (m, 4H, *β*-H), 9.09 (s, 1H, *β*-H), 9.28 (d, 1H, *β*-H, *J* 4.8 Hz).
MS (FAB^+) 803 $(M+H)^+$, 802 $M^{+\bullet}$.

2.7.4.11: Attempt to synthesize 2.18b from one pot reaction of porphyrin 2.15b

A solution of porphyrin **2.15b** (20 mg), *N*-methylglycine (22 mg, 10 equiv.) and DDQ (56 mg, 10 equiv.) in toluene (6 mL) was refluxed for 6 hours under a nitrogen atmosphere. TLC of the reaction mixture revealed that a new green product as only one spot. The solvent was evaporated, the residue was separated by column chromatography (silica gel) using a mixture of $CHCl_3$-light petroleum (1:1), the green compound **2.19b** (10.3 mg, 52% yield) was isolated.

mp > 300 ˚C.
UV-Vis ($CHCl_3$) λ_{max} (% rel. intensity) 374 (30%), 459 (100%), 528 (5%), 571 (7%), 623 (10%), 721 (7%) nm.

^{1}H NMR ($CDCl_3$) δ: -0.87 (s, 2H, N*H*), 7.30-7.38 (m, 4H, Ph-H), 7.55-7.69 (m, 4H, Ph-H), 8.13 (d, 1H, Ph-H, *J* 7.7 Hz), 8.32 (d, 1H, Ph-H, *J* 7.7 Hz), 8.57-8.65 (m, 4H, *β*-H), 8.68 (d, 1H, *β*-H, *J* 4.8 Hz), 9.15 (s, 1H, *β*-H), 9.31 (d, 1H, *β*-H, *J* 4.9 Hz).
MS (FAB^+) 803 $(M+H)^+$, 802 $M^{+\bullet}$.

2.7.4.12: Oxidative coupling of 2.15a by DDQ

A solution of porphyrin **2.15a** (20 mg) and DDQ (56 mg, 10 equiv.) in toluene (6 mL) was refluxed for 6 hours under a nitrogen atmosphere. TLC of the reaction mixture revealed that a new green product as only one spot. The solvent was evaporated, the residue was separated by column chromatography (silica gel) using a mixture of $CHCl_3$-light petroleum (1:1), the green compound **2.19a** (2.2 mg, 11% yield) was isolated (see **2.7.4.10**).

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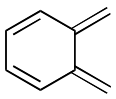
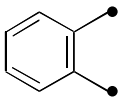
Chapter 3: Diels-Alder reactions of *meso*-tetraarylporphyrins with pyrazine *ortho*-quinodimethane

3.1: *o*-Quinodimethane and its heterocyclic analogues

Since the discovery of the Diels-Alder reaction in 1928, it became one of the most important carbon-carbon bond forming reactions available.[1] *o*-Quinodimethane (*o*QDM), also named *o*-xylylene **3.1**, and its derivatives have attracted extensive attention of both theoretical and synthetic chemists over the past decades.[2] The parent *o*-quinodimethane **3.1**, discovered by Cava *et al.* for the first time in 1957, is a reactive intermediate that dimerizes even at –150 ^{o}C. *o*QDMs are constituted by two diene units, one endocyclic and the other exocyclic, and theoretically both units can take part in a Diels-Alder reaction. However, the exocyclic diene unit is known to react preferably over the other one. *o*QDMs have a remarkable Diels-Alder reactivity as reactive dienes, but these intermediates can be trapped by a number of dienophiles. Although the reactivity of *o*QDM parallels that of a highly reactive diene, it may also be explained in terms of diradical structure **3.1a** in some reactions.[3]



3.1



3.1a

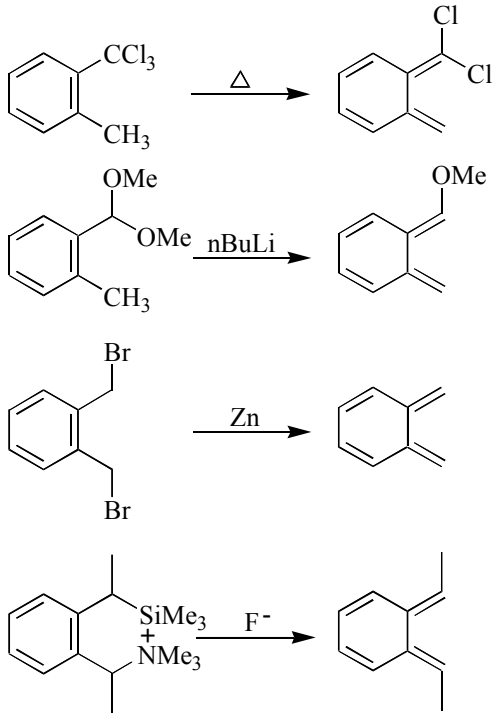
***o*-Quinodimethane**

*o*QDMs can be generated *in situ* by a number of routes which can be classified into four main types according to the different conditions: thermal, photochemical, electrochemical, and microwave generations.

According to the different precursors used, five generation methods can be listed as follows:

3.1.1: 1,4-Elimination of α,α'-substituted *o*-xylylenes

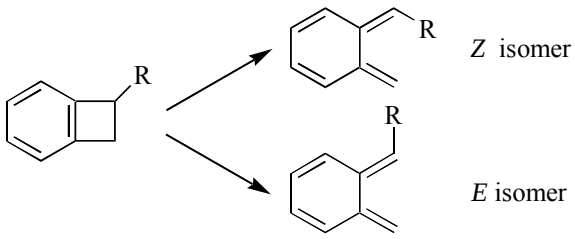
This process to generate *o*-quinodimethanes mainly involves thermal eliminations,[4] base-induced elimination,[5] reductive eliminations,[6] and ion induced eliminations[7] (Scheme 3.1).



Scheme 3.1

3.1.2: Thermolysis of benzocyclobutenes

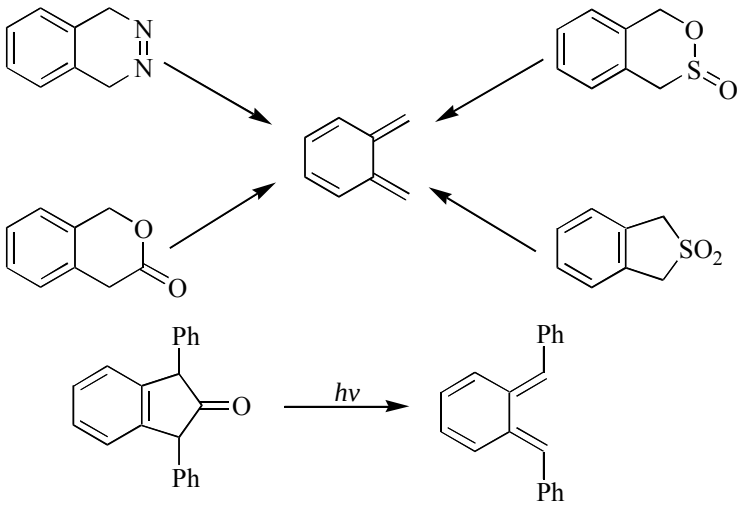
This transformation proceeds *via* a thermally allowed conrotatory electrocyclic ring-opening reaction. The sterically less hindered (*E*)-*o*-quinodimethanes will be generated preferentially for the derivatives bearing a substituent on the cyclobutene ring and they ring-open at a lower temperature than the unsubstituted benzocyclobutene (Scheme 3.2).[8] For R = NH_2, the ring opens at 25 ^oC, R = OH, at 80 ^oC, R = alkyl at 180 ^oC, R = H, at 200 ^oC.[2]



Scheme 3.2

3.1.3: Generated from benzo-fused heterocyclic compounds

This strategy involves the extrusion of a small molecule like nitrogen,[9] carbon dioxide,[10] and sulfur dioxide.[11] *o*-Quinodimethanes also can be generated photochemically from substituted 2-indanones by loss of carbon monoxide[12] (Scheme 3.3).

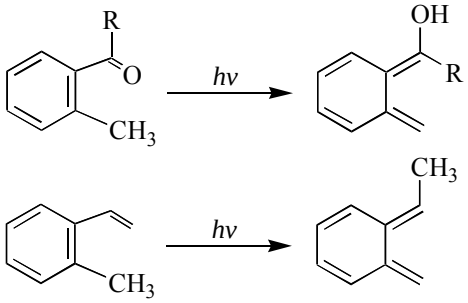


Scheme 3.3

3.1.4: Photoenolization and photorearrangement

An effective route to α-hydroxy-*o*-QDMs can be achieved by irradiation of *o*-alkylbenzaldehydes or *o*-alkylbenzophenones,[13] the process involves excitation to an nπ*

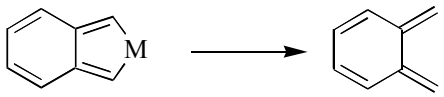
triplet state followed by intramolecular hydrogen abstraction to give a triplet diradical, which then decays to *E* and *Z* hydroxy-*o*-quinodimethanes. It is thought that *E* isomer has relatively longer life. The photolysis of *o*-alkylstyrenes has also been reported to produce *o*-quinodimethanes *via* a [1,5] sigmatropic rearrangement[14] (Scheme 3.4).



Scheme 3.4

3.1.5: Generation from *o*-xylylene-metal complexes

Transition metals are often used in stabilizing reactive organic molecules. *o*QDM can be generated from stable *o*-xylylene-metal complexes[15] (Scheme 3.5).



Scheme 3.5

Due to their considerable potential in synthesis, heterocyclic analogues **3.2** have also been explored.[16] The cycloaddition reactions involving heterocyclic *o*QDMs provide an attractive route to heteropolycyclic compounds.

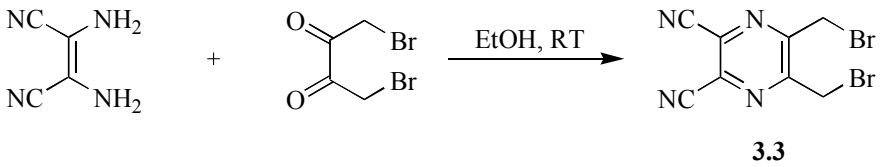
3.2 **3.2a**

Heterocyclic *o*-quinodimethane

3.2: Synthesis of the precursor of pyrazine *ortho*-quinodimethane

As part of our study of cycloaddition reactions of porphyrins, we decided to investigate the reactivities of *meso*-tetraarylporphyrins with heterocyclic *ortho*-quinodimethanes. However, we found very low reactivities of *meso*-tetraarylporphyrins with pyrimidine *ortho*-quinodimethane.[17] Recently, pyrazine *ortho*-quinodimethanes have been used in the functionalization of fullerene.[18] We then tried to synthesize the precursor of pyrazine *ortho*-quinodimethane and investigate its reactivity with *meso*-tetraarylporphyrins.

Bis(bromomethyl)pyrazine **3.3** was prepared in 71% yield by the condensation of diaminomaleonitrile with one equivalent of 1,4-dibromo-2,3-butanedione in ethanol at room temperature (Scheme 3.6). It is a white solid, the ^{1}H NMR shows a singlet at δ 4.76 ppm.

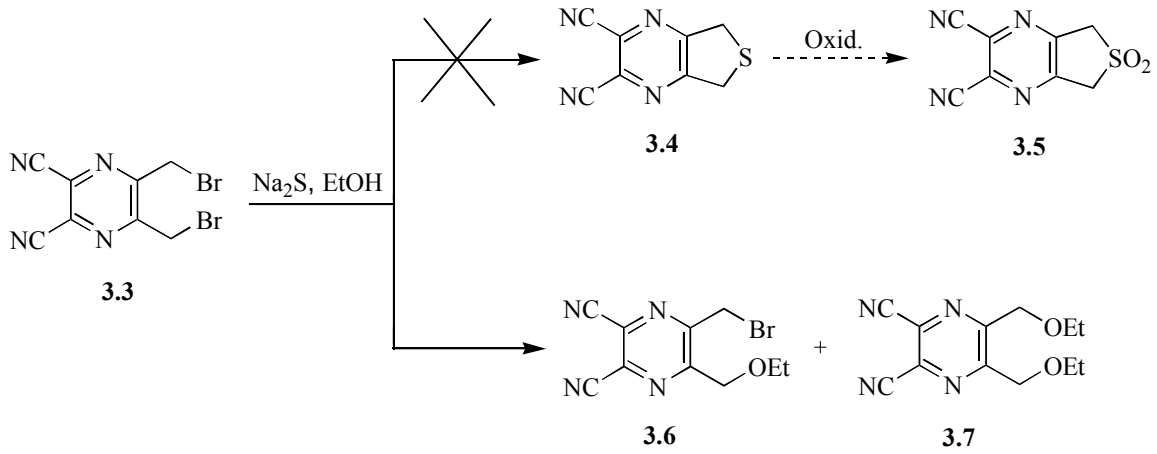


3.3

Scheme 3.6

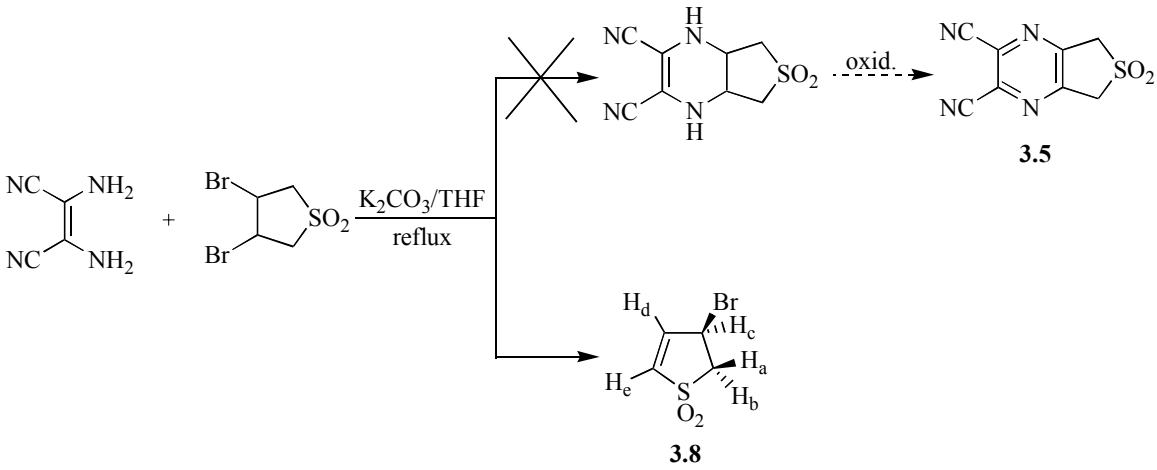
It is well known that pyridine can react with benzyl bromide yielding the corresponding pyridinium salt. However, bis(bromomethyl)pyrazine **3.3** was reasonably stable, its solution turned yellow at high temperature (but no salt precipitates), and TLC showed that it was still **3.3**. This means that the nucleophilicity of **3.3** is smaller than that of pyridine.

The precursors of *ortho*-quinodimethanes used in our reactions with porphyrins are the sulfones (see Introduction section). The preparation of sulfone **3.5** was planned as shown in Scheme 3.7. However, when a colleague tried to convert the bis(bromomethyl)pyrazine **3.3** into dihydrothiophene derivative **3.4** by reaction with sodium sulfide, in ethanol and at room temperature, only the ethoxymethyl derivatives **3.6** and **3.7** were formed *via* nucleophilic substitution of the bromine atoms by alkoxy groups.[19]



Scheme 3.7

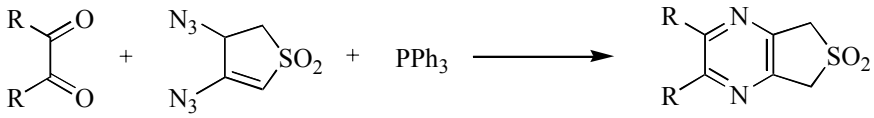
We then tried to prepare the sulfone **3.5** by the reaction of diaminomaleonitrile with 3,4-dibromosulfolane with subsequent oxidative aromatization (Scheme 3.8). But the reaction was very complicated. The elimination compound **3.8** was isolated as the main product in 29% yield. It has been shown that treatment of 3,4-dibromosulfolane with strong bases gives a mixture of products.[20]



Scheme 3.8

Chou *et al.* also tried to prepare the sulfone **3.5** by this way, but they found the reaction produced a complex mixture containing no desired product.[21] Chou *et al.* synthesized the pyrazine-fused 3-sulfolenes **3.10a-c** from diazido-2-sulfolene **3.9** (Scheme 3.9). They found that compounds **3.10a-c** loose SO_2 only at temperatures above 290 ^oC, indicating

that the generation of pyrazine *ortho*-quinodimethanes from sulfones **3.10a-c** is very difficult.[21]

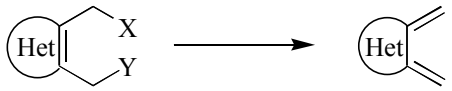


3.9 **3.10**

a, R = H
b, R = CH_3
c, R = -$(CH_2)_4$-

Scheme 3.9

A large number of heterocyclic *o*-quinodimethanes **3.2** have been produced by the 1,4-elimination from α,α'-substituted heterocycle derivatives **3.11** (Scheme 3.10).[16] The most used derivatives are the dibromo compounds which react with sodium iodide at temperatures ranging from room temperature to 150 ^oC to afford the *o*QDM **3.2**. We also used bis(bromomethyl)pyrazine **3.3** as the precursor of pyrazine *ortho*-quinodimethane.



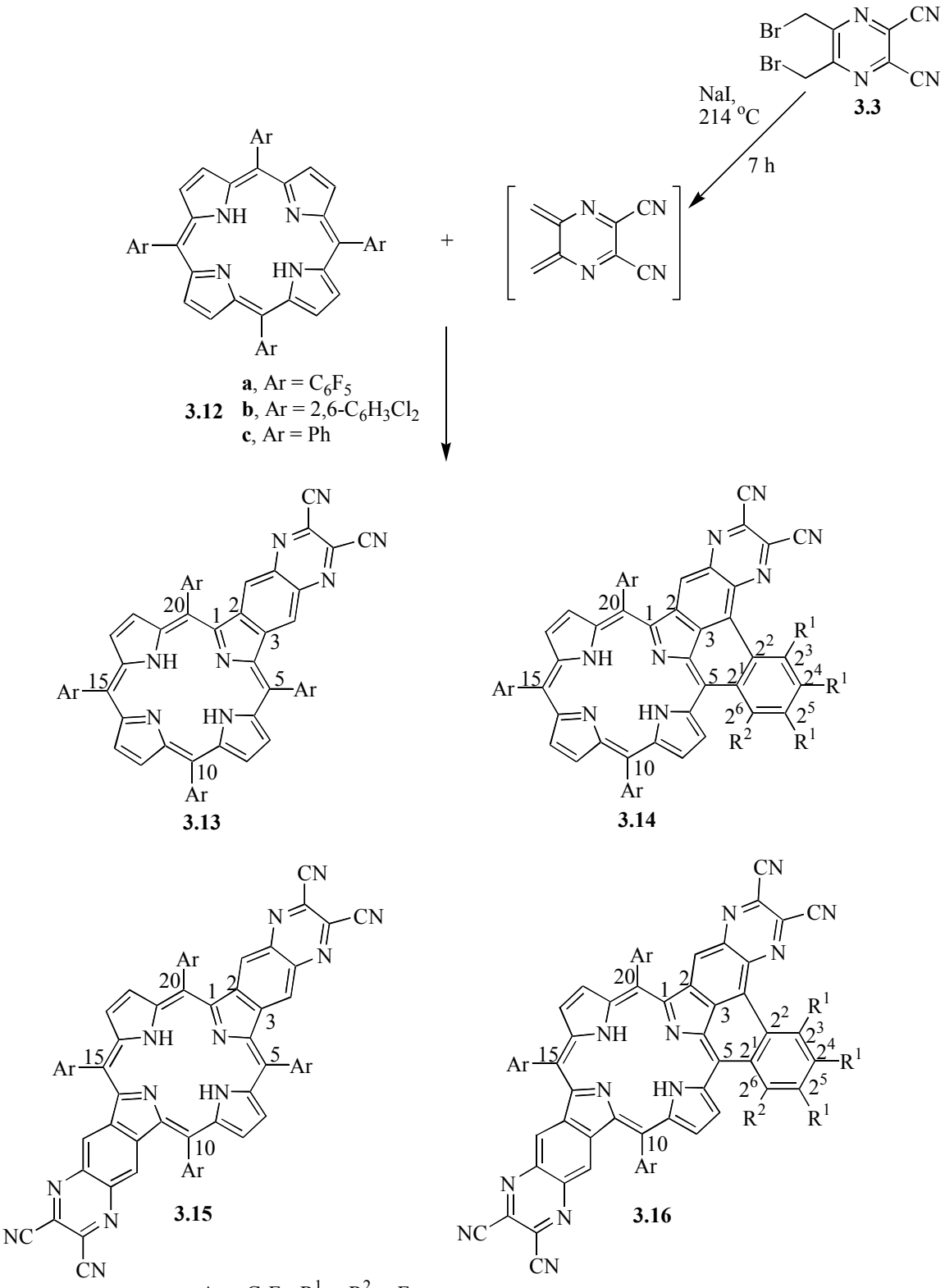
3.11 **3.2**

X = H, Y = Cl, OCOR
X = halogen, Y = halogen
X = R_3N^+, Y = $SiMe_3$
X = $SnBu_3$, Y = OAc

Scheme 3.10

3.3: Diels-Alder reactions of *meso*-tetraarylporphyrins with pyrazine *ortho*-quinodimethane

Compared to other Diels-Alder reactions involving porphyrins as dienophiles, it seems that high temperatures are necessary for such [4+2] cycloaddition reactions due to the low reactivity of porphyrins. So, we performed the reactions of *meso*-tetraarylporphyrins **3.12**, with ten equivalents of bis(bromomethyl)pyrazine **3.3**, and thirty equivalents of sodium iodide in refluxing 1,2,4-trichlorobenzene (214 ^oC) for 7 hours (Scheme 3.11).



a, Ar = C_6F_5, $R^1 = R^2 = F$
b, Ar = 2,6-$C_6H_3Cl_2$, $R^1 = H$, $R^2 = Cl$
c, Ar = Ph, $R^1 = R^2 = H$

Scheme 3.11

For TPFPP **3.12a**, a TLC of the reaction mixture revealed some unchanged starting porphyrin and four new compounds. The resulting mixture was separated by column chromatography (silica gel) into three fractions using a gradient of chloroform/light petroleum as eluent. The first fraction was the unchanged TPFPP (18%) and the second one was shown to be a mixture of mono-addition compounds **3.13a** and **3.14a**, which were then separated by preparative TLC. The third fraction was also a mixture of two compounds which after being separated by preparative TLC were identified as the bis-addition compounds **3.15a** and **3.16a**. These four new compounds show different absorbance features: **3.13a** is brown, **3.14a** is yellow, **3.15a** is green and **3.16a** is red. We also tried the same reaction in refluxing toluene, but almost all the starting TPFPP was recovered, only a trace of **3.13a** was formed.

The structures of the new compounds were deduced from their UV-Vis, ^{1}H, ^{13}C NMR and mass spectra. The main product **3.13a** displays C_2 symmetry. It is very clear from its ^{1}H, ^{13}C NMR spectra there are no sp^3 carbons (and the corresponding protons) ruling out the structure of chlorin. In the ^{1}H NMR spectrum, the singlet at δ 8.29 ppm corresponds to the two quinoxaline protons and the singlet at δ 8.76 ppm corresponds to two β-pyrrolic protons H-12 and H-13. Finally, the four β-pyrrolic protons H-7, H-8, H-17, H-18 appear as two doublets at δ 8.95 (*J* 5.1 Hz) and 9.04 ppm (*J* 5.1 Hz). The ^{13}C NMR spectrum shows only 14 signals, which correspond to 'half' of the molecule [note that the carbons of the C_6F_5 groups appear as small signals (multiplets, δ 114.9-148.2 ppm) due to the coupling with fluorine atoms and to the long relaxation times]. The FAB mass spectrum of **3.13a** shows intense peaks at *m/z* 1127 ($[M+H]^+$) and 1126 ($[M]^{+\bullet}$) while its UV-Vis spectrum shows a pronounced red shift of both Soret and Q bands (λ_{max} 379, 425, 525, 564, 608, 662 nm) relative to TPFPP, as expected for a porphyrin with an extended conjugation of the π-system.

Compound **3.14a** has an interesting structure, resulting from a cyclization reaction between the *meso*-aryl group and the β-fused quinoxaline ring. Its mass spectrum shows intense peaks at *m/z* 1107 ($[M+H]^+$) and 1106 ($[M]^{+\bullet}$), which means that one HF molecule has been eliminated from **3.13a**. The ^{1}H NMR spectrum (Figs 3.1, 3.2), shows two signals at δ -1.49 and -1.20 ppm corresponding to the NH protons and one singlet at δ 8.47 ppm corresponding to the quinoxaline proton. The β-pyrrolic protons H-12 and H-13 appear as an AB spin system at δ 8.68 ppm (*J* 5.0 Hz), while the protons H-17 and H-18 appear as

two doublets at δ 8.83 ppm (*J* 5.0 Hz) and 8.94 ppm (*J* 5.0 Hz). The β-pyrrolic proton H-8 appears as a doublet at δ 8.79 ppm (*J* 5.0 Hz) and, surprisingly, H-7 appears as a double doublet at δ 9.47 ppm (*J* 5.0 Hz and 11.2 Hz); this spliting is due to the through-space coupling with the *o*-fluorine atom of the adjacent *meso*-aryl group. 'Through-space' or 'proximate' spin-spin coupling between fluorine and other magnetic nuclei (^{1}H, ^{13}C, ^{19}F) has already been firmly established as an NMR phenomenon.[22] Indirect (scalar) coupling of nuclear spins is normally propagated by polarization of the spins of the intervening bonding electrons. The efficiency of nuclear spin-spin coupling depends on the number and bond orders of the intervening bonds and upon their geometrical arrangement and it may be altered by the effect of substituents. Unusual large coupling constants may be observed for certain nuclei when they are many bonds apart but physically close in space. The UV-Vis spectrum of **3.14a** shows a pronounced red shift of both Soret and Q bands (λ_{max} 388, 439, 482, 651, 707 nm) relatively to **3.13a**, confirming that it is a porphyrin with an extended π-system due to the conjugation with the fused *meso*-phenyl ring. The loss of symmetry leads to a splitting of Soret band (as a consequence, we could observe a widening of the band or shoulder).[23]

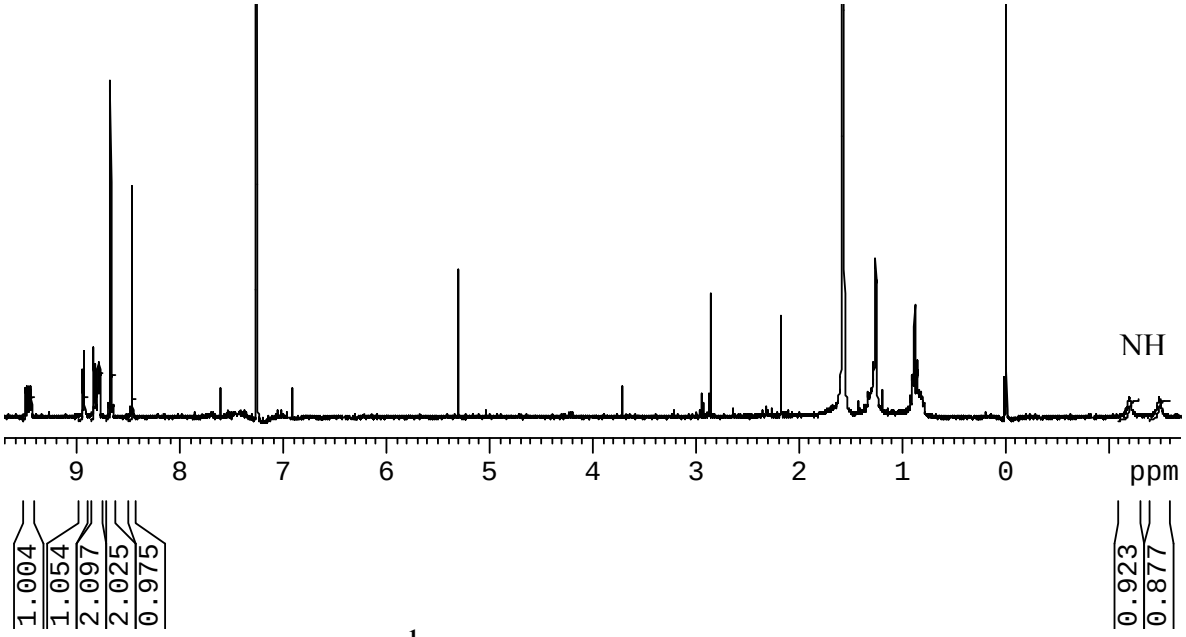


Figure 3.1: ^{1}H NMR spectrum of compound 3.14a

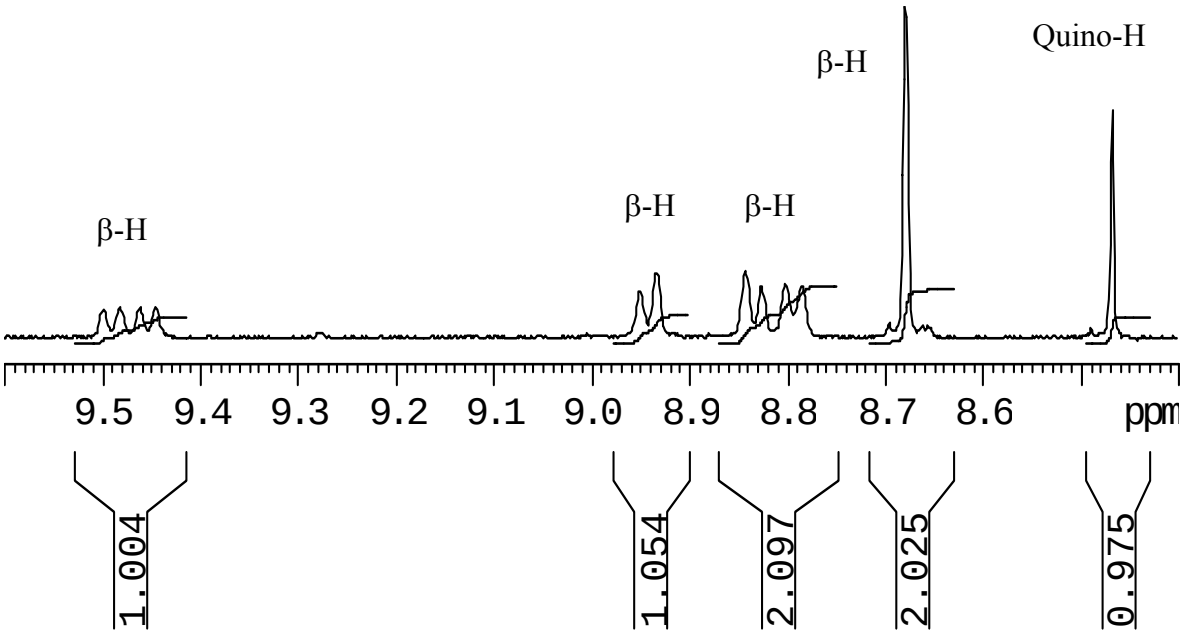


Figure 3.2: ^{1}H NMR spectrum of compound 3.14a (aromatic region)

The mass spectrum of **3.15a** shows a intense peak at *m/z* 1279 ($[M+H]^+$) which indicates that it is a bis-addition compound. Its ^{1}H NMR spectrum shows only three singlets: one at δ -2.42 ppm corresponding to the N*H* protons, one at δ 8.27 ppm corresponding to the four quinoxaline protons, and another one at δ 8.96 ppm corresponding to the four β-pyrrolic protons. It is evident from this ^{1}H NMR spectrum that **3.15a** resulted from a site specific bis-addition to opposite pyrrolic rings and not to adjacent pyrrolic rings. It is in agreement with the reaction of TPFPP with *ortho*-benzoquinodimethane **3.1** (see Introduction section) and other previous studies. Callot[24] and Cavaleiro *et al.*[25] also observed the site specific bis-addition occurring in opposite pyrrolic rings, since some theoretical studies and experimental findings show that the two opposite β- β' double bonds in free-base porphyrins possess more stable double bond character.[26]

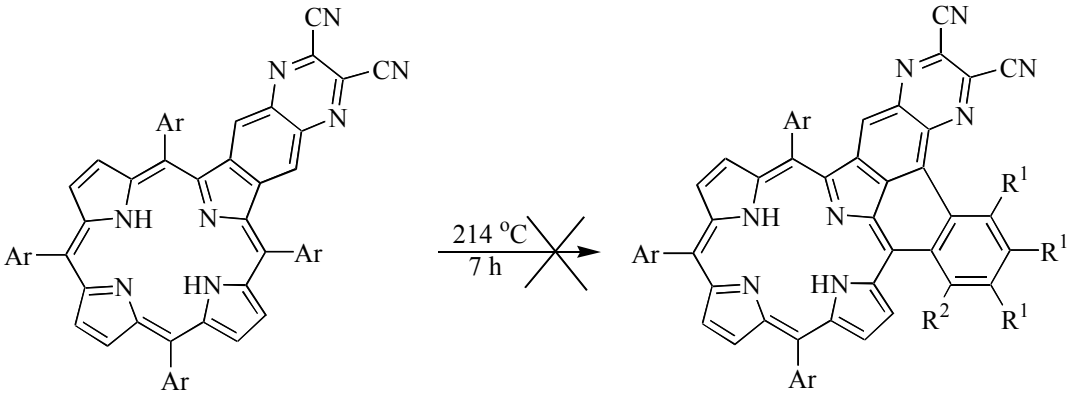
The mass spectrum of compound **3.16a** shows a intense peak at *m/z* 1259 ($[M+H]^+$). Its ^{1}H NMR spectrum shows that the β-pyrrolic proton H-7 appears as a double doublet of doublets at δ 9.48 ppm (*J* 1.7, 5.0 and 10.4 Hz), also due to the through-space coupling with the *o*-fluorine atom of the *meso*-aryl groups (*J* 10.4 Hz), coupling with inner N*H* (*J*

1.7 Hz) and with protonH-8. Proton H-8 appears as a broad doublet at δ 8.72 ppm (*J* 5.0 Hz) due to the small coupling with N*H* (responsible for the broadening of the signal), while H-17 and H-18 appear as an AB spin system (δ 8.898 and 8.899 ppm, *J* 4.8 Hz). The two singlets at δ -1.42 and -1.03 ppm correspond to the N*H* protons are observed. The UV-Vis spectrum of **3.16a** shows a sizable absorption at 744 nm and split Soret bands at 440 and 497 nm also due to the extended conjugation of the π-system.

Quite similar results were obtained when we used porphyrin **3.12b** (Table 3.1). In this case, the formation of compounds **3.14b** and **3.16b** resulted from the elimination of one HCl molecule from **3.13b** and **3.15b**, respectively. Since porphyrin **3.12c** is much less reactive as a dienophile than **3.12a** and **3.12b**, and there are no halogen atoms at the *meso*-phenyl group, we expected to obtain only the mono-addition product **3.13c**. However, surprisingly, together with a small amount of **3.13c**, **3.14c** was also formed as the main product. In this case, since the formation of **3.14c** could not result from an elimination reaction, it must be formed by an oxidative coupling reaction. Attempted formation of **3.14** by refluxing **3.13** in 1,2,4-trichlorobenzene was unsuccessful (Scheme 3.12). Also, refluxing **3.13c** in chloroform in the presence of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) **3.14c** was not formed (Scheme 3.13). These experiments seem to indicate that the coupling process occurs before the aromatization of the Diels-Alder adduct. From ^{1}H NMR of **3.14b** and **3.14c** (Figs 3.3-3.6), through-space coupling were not observed since R^2 is a proton or chlorine atom. These cycloaddition products may be useful as the precursors for the synthesis of β-fused porphyrinophthalocyanines (analogues of β-fused porphyrin oligomers described by Smith *et al.*).[27]

Table 3.1 Comparative reactivity and product yields of *meso*-tetraarylporphyrins with pyrazine-*o*-quinodimethane

meso-aryl group	Recovered starting porphyrin(%)	Yield (%)			
		3.13	**3.14**	**3.15**	**3.16**
a C_6F_5	18	34	3	6	1
b 2,6-$C_6H_3Cl_2$	11	36	4	7	2
c Ph	14	3	16	-	-



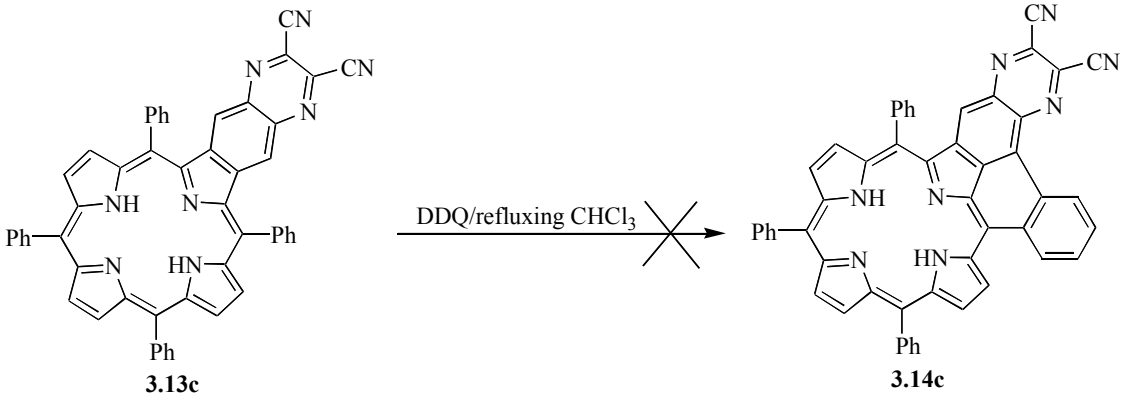
3.13 **3.14**

a, Ar = C_6F_5, $R^1 = R^2 = F$

b, Ar = 2,6-$C_6H_3Cl_2$, R^1 = H, R^2 = Cl

c, A r = Ph, $R^1 = R^2 = H$

Scheme 3.12



3.13c **3.14c**

Scheme 3.13

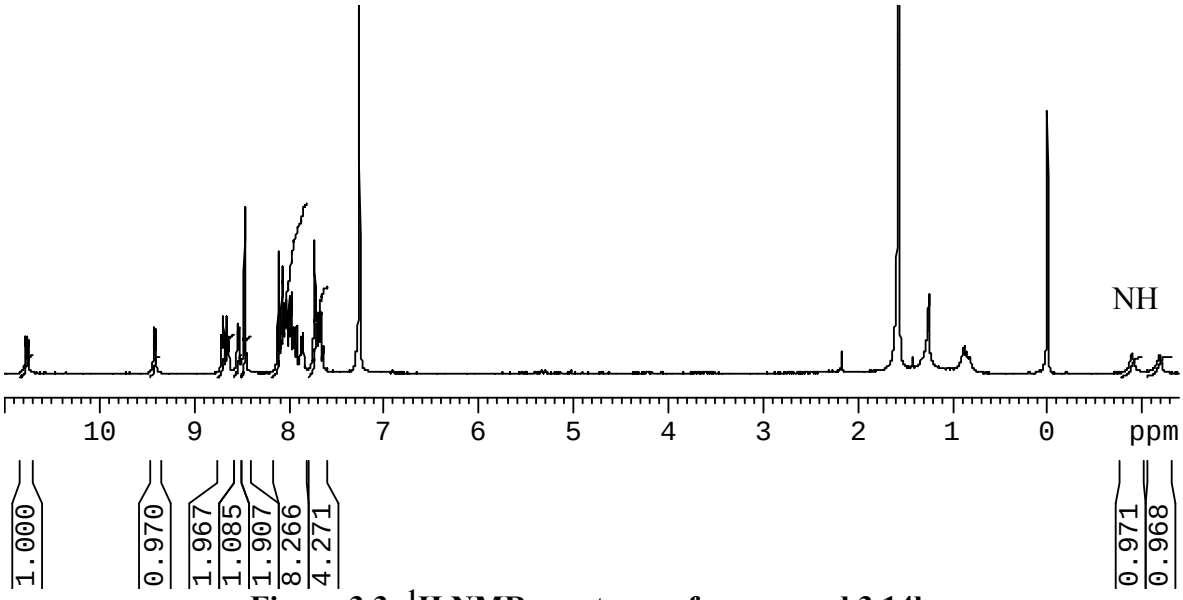


Figure 3.3: ^{1}H NMR spectrum of compound 3.14b

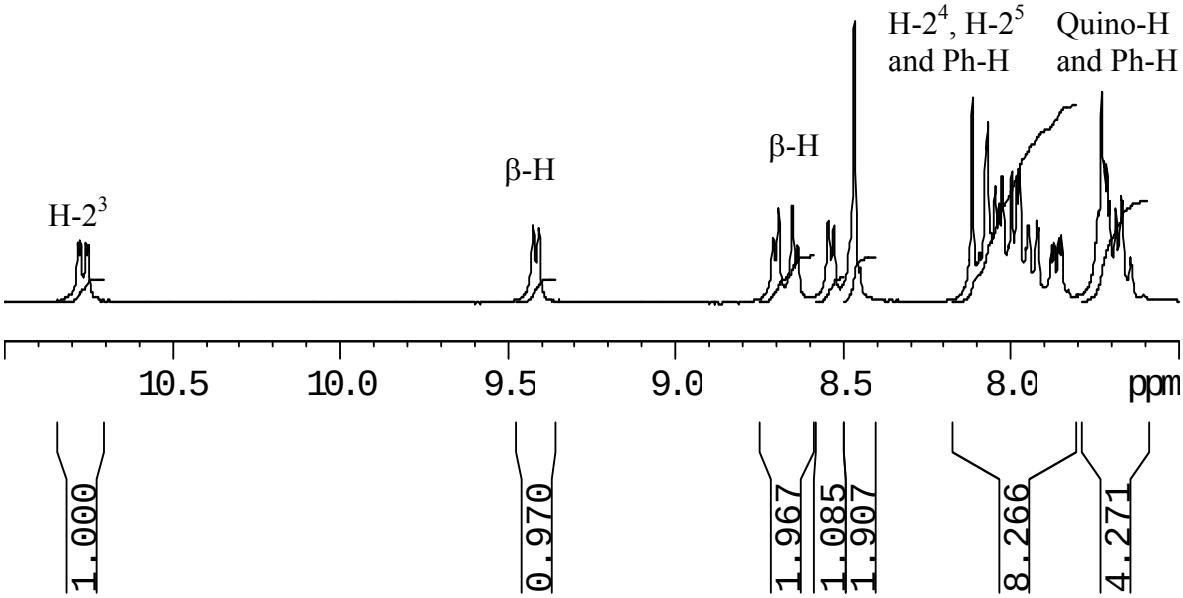


Figure 3.4: ^{1}H NMR spectrum of compound 3.14b (aromatic region)

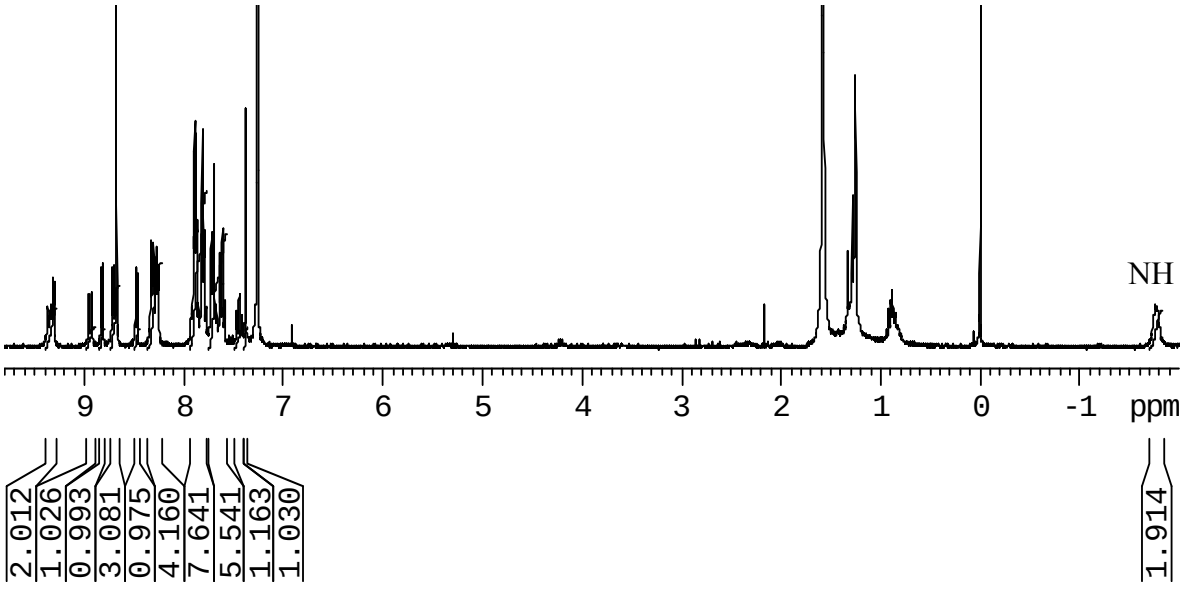


Figure 3.5: ^{1}H NMR spectrum of compound 3.14c

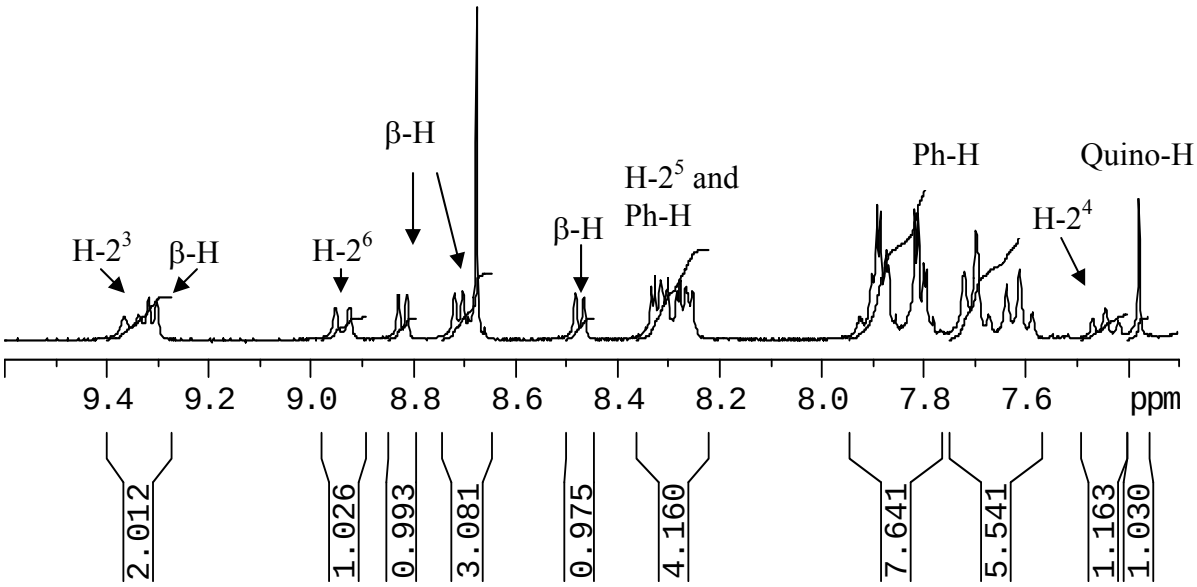
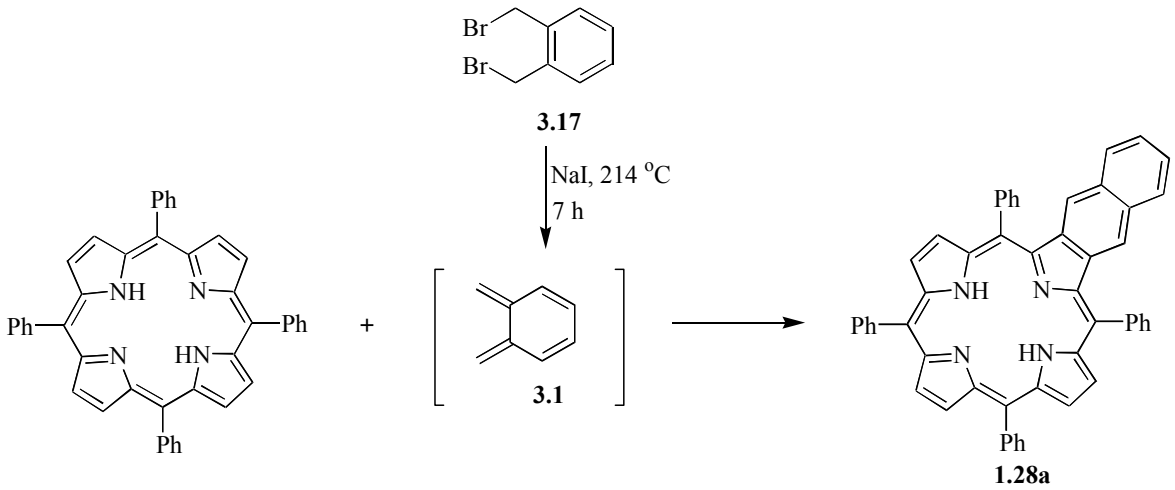
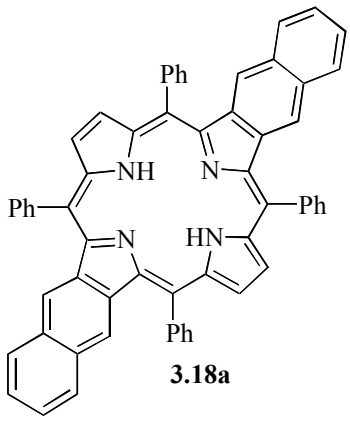


Figure 3.6: ^{1}H NMR spectrum of compound 3.14c (aromatic region)

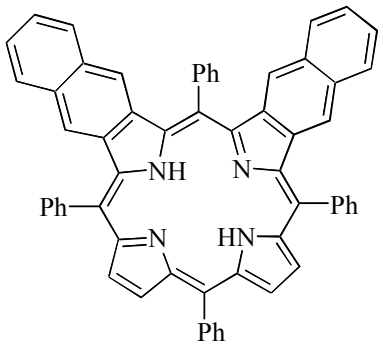
In contrast to the Diels-Alder reactions of porphyrins with *o*QDM **3.1** generated from 1,3-dihydrobenzo[*c*]thiophene-2,2-dioxide (Scheme 1.6), we obtained these *meso*+β fused porphyrins instead of the expected chlorins. Since the two *o*QDMs are generated from different types of precursors, we have reinvestigated the reaction of TPP with *o*QDM **3.1** generated *in situ* by the 1,4-elimination of α,α'-dibromo-*o*-xylene **3.17** (Scheme 3.14). When the reaction was carried out, the TLC of the reaction mixture revealed two new compounds together with unchanged TPP. The polarities of three compounds are very similar, but we were able to separate them by preparative TLC. Naphtho[2,3-*b*]porphyrin **1.28a**[17] was obtained in 4% yield. The mass spectrum of the other trace compound shows a intense peak at *m/z* 815 ($[M+H]^+$), indicating that it is an oxidized bis-addition compound, probably **3.18a** or **3.18b**. The UV-Vis spectrum shows a pronounced red shift of both Soret and Q bands (λ_{max} 452, 526, 562, 611, 668, 764 nm) relative to **1.28a**, also confirming an extended conjugation of the π-system. However, the cyclization product **3.19** between the β-fused naphthalene ring and the adjacent *meso*-phenyl group was not obtained.



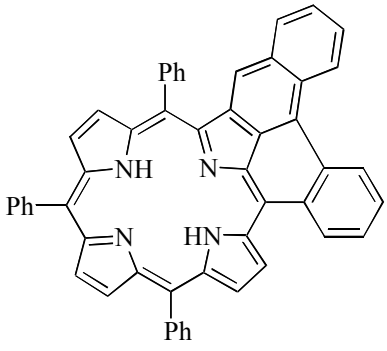
Scheme 3.14



3.18a



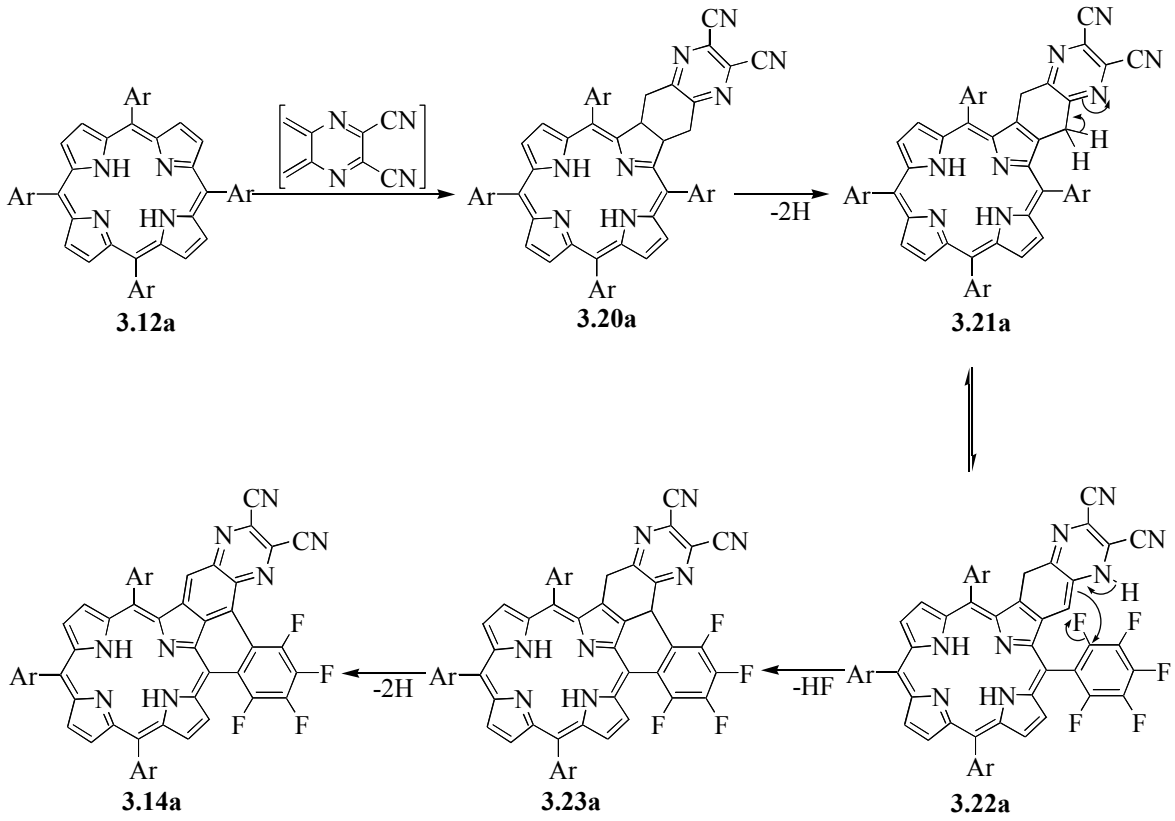
3.18b



3.19

Based on these studies, a proposed mechanism is shown in Scheme 3.15. The oxidation of chlorin **3.20a**, the cycloaddition reaction adduct, afforded porphyrin **3.21a** which has an imine structure. Porphyrin **3.21a** can isomerizate to porphyrin **3.22a** which has an enamine structure and an extended conjugation. It is well known that the β-carbon of enamine has

nucleophilic reactivity. Therefore, porphyrin **3.14a** can be obtained *via* the aromatization of the nucleophilic ring-closing product **3.23a**.



Scheme 3.15

These novel polycyclic compounds **3.14a-c**, **3.16a** and **3.16b** have very interesting UV-Vis absorption properties with bands at 700-800 nm – the far end of the visible spectrum (Fig. 3.7). The new generation PDT photosensitizers need strong absorptions near or above 700 nm because of the greater tissue penetration of light with longer wavelengths.[28] Near-infrared (NIR) laser protective dyes and organic light-emitting diodes (OLEDs) that function in the NIR region have attracted increased attention for the applications relevant to sensing, optoelectronics and communications.[29] NIR electroluminescence devices based on porphyrins have also been reported.[30] The two stereoisomeric bacteriochlorins **1.30** (*cis* and *trans*) have strong bands at 747 and 761 nm, but the yields are very low. These yields of these new *meso*+β fused polycyclic aromatic compounds, especially **3.14c** (16%), are quite good, and these compounds may be considered as potential PDT photosensitizers and NIR materials.

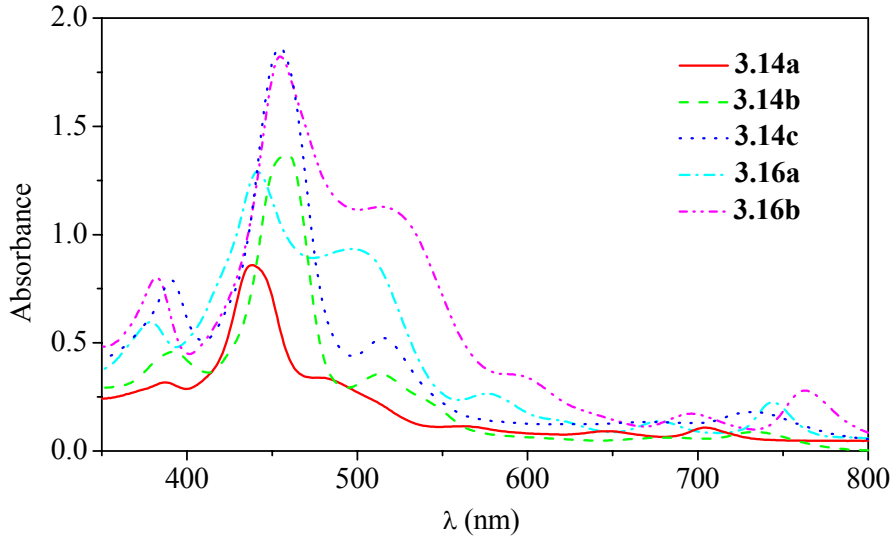
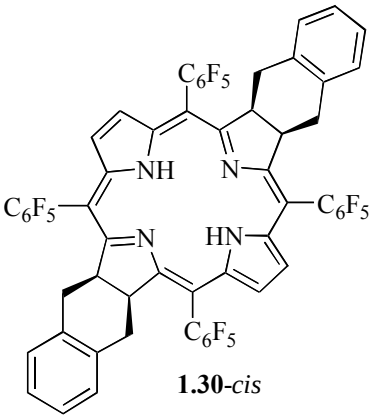
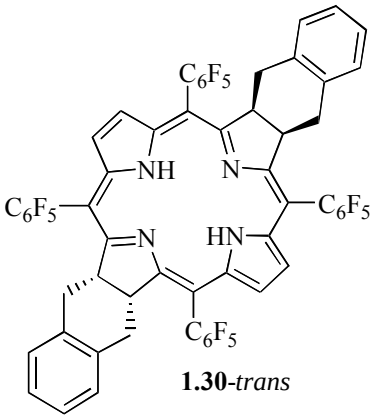


Figure 3.7: UV-Vis spectra of *meso*+β fused π-extended porphyrins

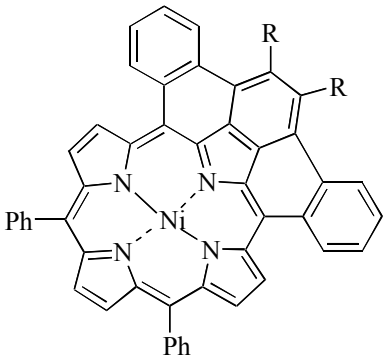


1.30-*cis*

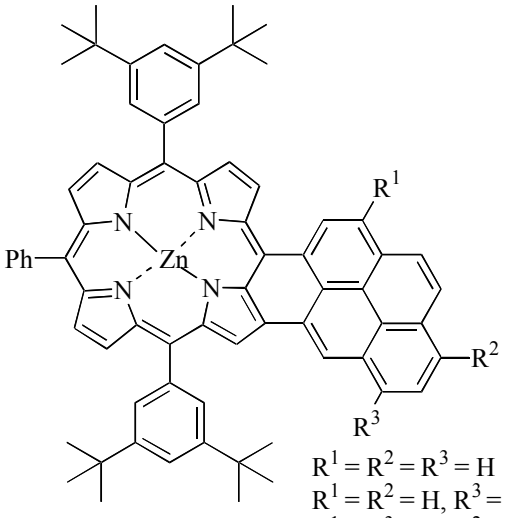


1.30-*trans*

Recently, Smith *et al.*[31] and Zaleski *et al.*[32] synthesized picenoporphyrins **3.24** from the Bergman cyclization of porphyrinic-enediynes. Pyrene-fused porphyrins **3.25** were also prepared *via* oxidative ring closure reactions (Scholl reaction) on *meso*-pyrenylporphyrins.[33] These porphyrins have also novel *meso*+β fused polycyclic aromatic structures (these fused rings are six-membered, those *meso*+β fused porphyrins with five-membered fused rings will be discussed in the chapter about cycloaddition reactions of pyridinium *N*-ylides). We believe more *meso*+β fused π-extended prophyrins will be exploited in the future.



3.24 R = H, Bu, Ph



3.25

$R^1 = R^2 = R^3 = H$
$R^1 = R^2 = H$, $R^3 = O^nBu$
$R^1 = R^3 = H$, $R^2 = O^nBu$
$R^1 = R^2 = O^nBu$, $R^3 = H$
$R^1 = R^3 = O^nBu$, $R^2 = H$
$R^1 = R^2 = R^3 = O^nBu$

3.4: ESI mass spectrometry studies of reaction products of *meso*-tetraarylporphyrins with pyrazine *ortho*-quinodimethane

ESI mass spectrometry studies of all reaction products revealed similar MS/MS spectra. The main collisionally induced fragmentation pathway observed in these spectra corresponds to the loss of one or two *meso*-aryl moieties (Fig. 3.8-3.17) which is also a characteristic fragmentation of the *meso*-tetraphenylporphyrins.[34] Another major fragmentation observed for the cycloaddition products of TPFPP **3.12a** corresponds to the successive loss of HF (Fig. 3.8-3.11). The cycloaddition products of *meso*-tetrakis(2,6-dichorophenyl)porphyrin (TDCPP) **3.12b** show successive loss of HCl (Fig. 3.12-3.15). The ES-MS spectra of the bis-addition compounds of TPFPP show the $[M+2H]^+$ ion as the major ion of the molecular envelope (Fig. 3.18). The formation of reduced $[M+nH]^+$ ions, mainly n = 2, 3 were observed in FAB-MS spectra of porphyrins.[35] Formation of reduced species in dimers of porphyrins occurred mainly when an acidic FAB matrix was used. Reduction reactions are easily rationalized to occur under FAB ionization, since protons, electrons and other reactive species are known to be formed under FAB ionization process. This is not true for the electrospray ionization process. The formation of the reduced ions

under ES ionization, can be explained by the initial formation of a doubly charged species $[M+2H]^{2+}$ by uptake of two protons by the porphyrinic moiety, followed by capture of electrons that are present in solution due to electrochemical processes and formation a stable $[M+2H]^{+}$ ion. The existence in the porphyrin ring of several basic sites allows the easy formation of the doubly charged species. The presence of other groups with electron affinity also facilitates the electron capture.

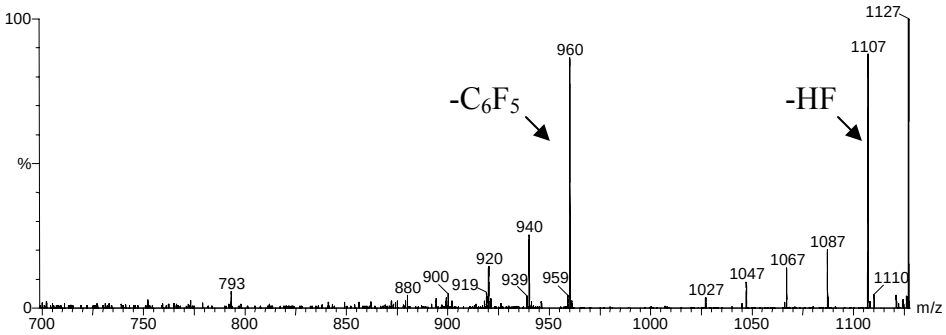


Figure 3.8: ESI-MS/MS spectrum of compound 3.13a

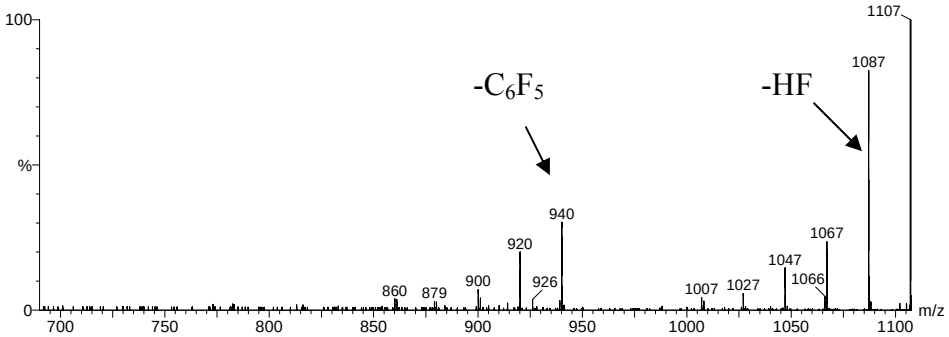


Figure 3.9: ESI-MS/MS spectrum of compound 3.14a

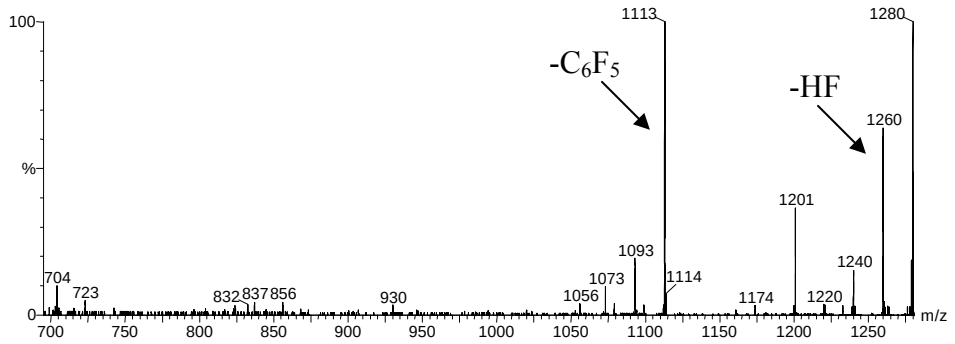


Figure 3.10: ESI-MS/MS spectrum of compound 3.15a

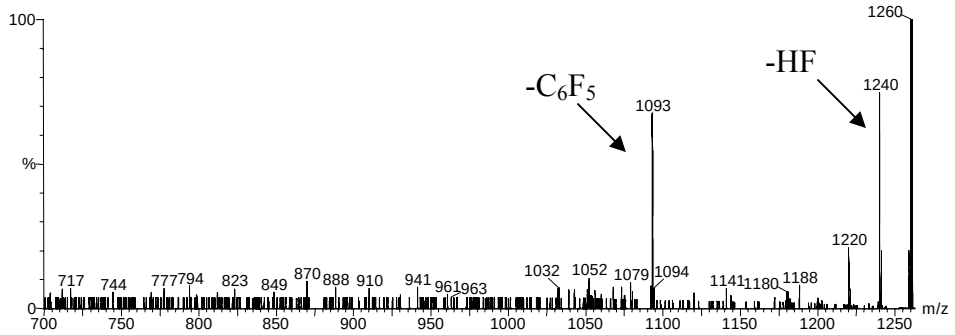


Figure 3.11: ESI-MS/MS spectrum of compound 3.16a

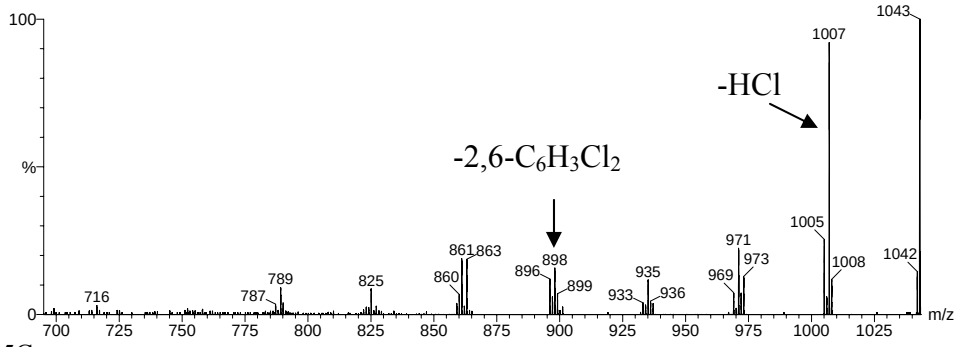


Figure 3.12: ESI-MS/MS spectrum of compound 3.13b

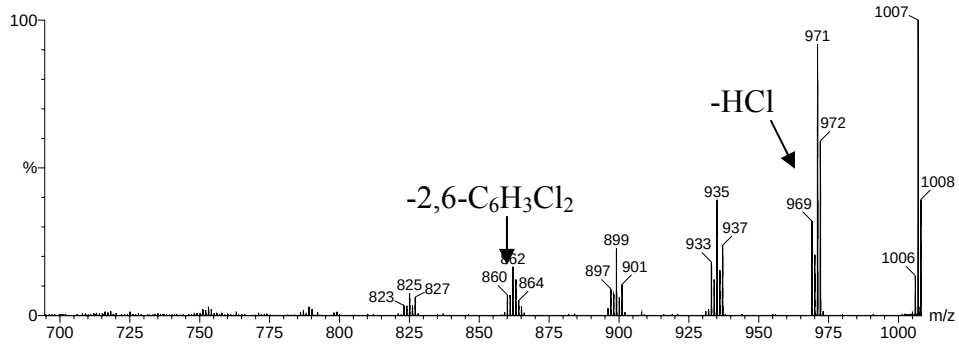


Figure 3.13: ESI-MS/MS spectrum of compound 3.14b

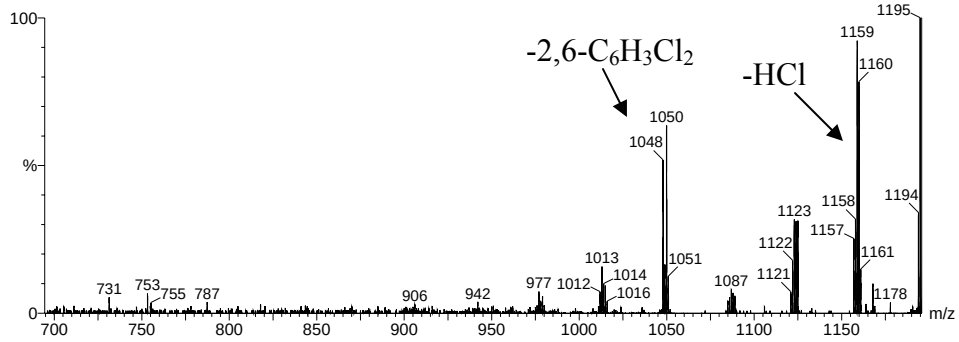


Figure 3.14: ESI-MS/MS spectrum of compound 3.15b

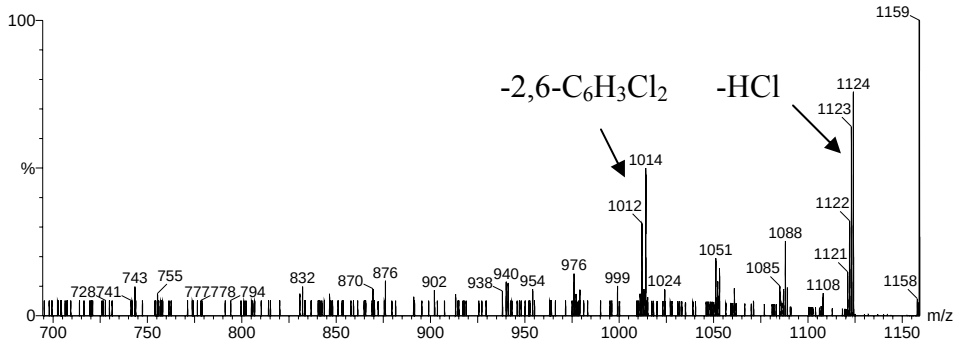


Figure 3.15: ESI-MS/MS spectrum of compound 3.16b

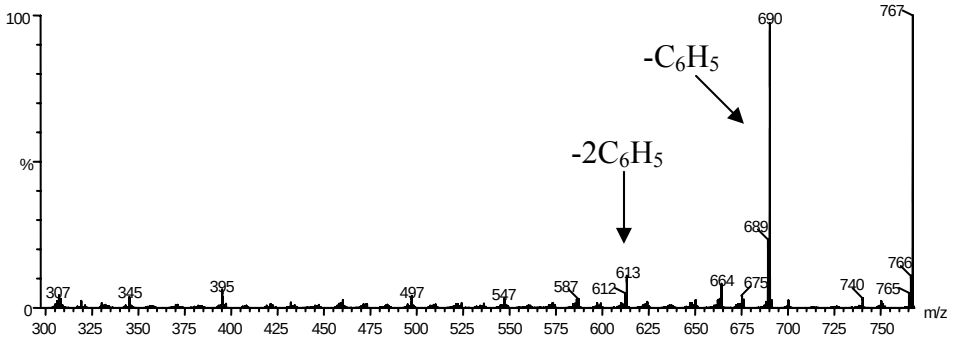


Figure 3.16: ESI-MS/MS spectrum of compound 3.13a

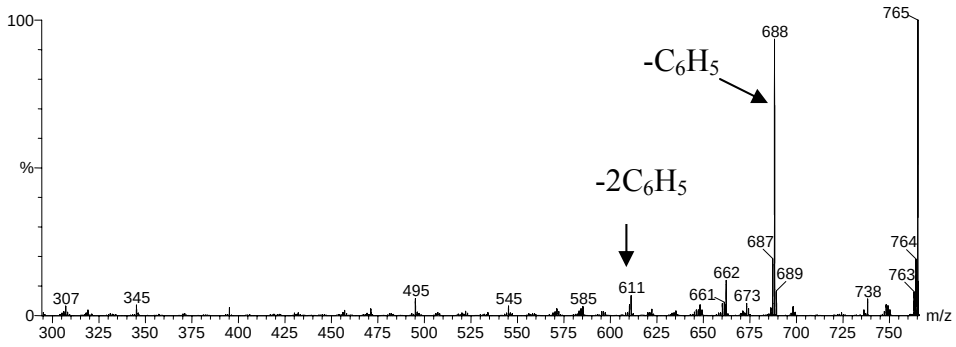


Figure 3.17: ESI-MS/MS spectrum of compound 3.14a

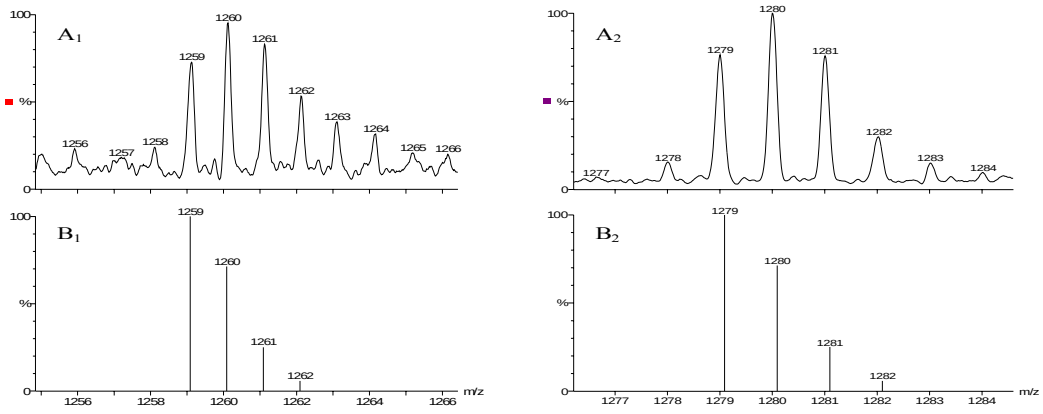


Figure 3.18: Partial ES-MS spectra of porphyrins 3.16a (A_1) and 3.15a (A_2), showing the molecular ion envelope region. Calculated isotopic contribution for the $[M+H]^+$ ions of porphyrins 3.16a (B_1) and 3.15a (B_2).

The formation of the reduced ions only in the bis-addition compounds case could be due to the presence of the additional nitrogens, reflecting more sites able for protonation. Also, in these porphyrins, fluorines are the electron affinity moieties that uptake the electrons.

The higher number of electron affinity sites in the porphyrins **3.15a** and **3.16a** can justify the observation of the reduced ions only for the bis-addition compounds **3.15a** and **3.16a**, and not for the other two bis-addition compounds **3.15b** and **3.16b** (Fig. 3.19).

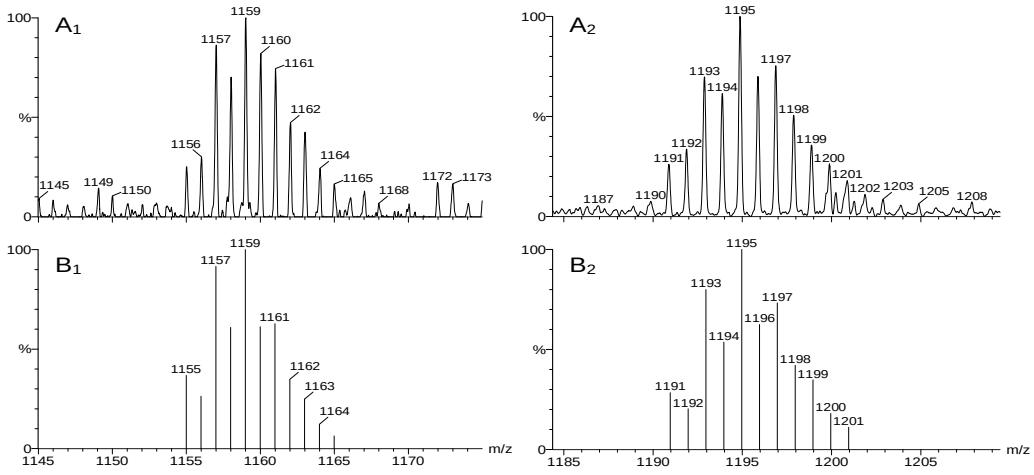


Figure 3.19: Partial ES-MS spectra of porphyrins 3.16b (A_1) and 3.15b (A_2), showing the molecular ion envelope region. Calculated isotopic contribution for the $[M+H]^+$ ions of porphyrins 3.16b (B_1) and 3.15b (B_2).

3.5: Conclusion

In conclusion, the Diels-Alder reactions of *meso*-tetraarylporphyrins with pyrazine *o*-quinodimethane afforded the π-extended porphyrins instead of the expected chlorin adducts. The bis-addition is site specific, occurring in opposite pyrrolic rings. The novel *meso*+β fused polycyclic aromatic compounds result from coupling reaction between the β-fused quinoxaline ring and one adjacent *meso*-aryl group. These π-extended porphyrins have very interesting UV-Vis absorption properties with bands at the far end of the visible

spectrum (700-800 nm), that is, near infrared (NIR) region. Therefore, these π-extended porphyrins have potential biomedical or materials applications.

These products could be used as the precursors for the synthesis of β-fused porphyrinophthalocyanines.

3.6: Experimental Section

3.6.1: General

Melting points were measured on a Reichert Thermovar apparatus fitted with a microscope and are uncorrected. ^{1}H, and ^{13}C NMR spectra were recorded on a Bruker Avance 300 spectrometer at 300.13 and 75.47 MHz, respectively. $CDCl_3$ was used as solvent and TMS as internal reference; the chemical shifts are expressed in δ (ppm) and the coupling constants (*J*) in Hertz [Hz]. Unequivocal ^{1}H assignments were made with aid of 2D COSY ($^{1}H/^{1}H$) and NOESY spectra (mixing time of 800 ms), while ^{13}C assignments were made on the basis of 2D HSQC and HMBC (delays for long-range *J* C/H couplings were optimized for 7 Hz) experiments. Mass spectra and HRMS spectra were recorded on VG AutoSpec Q and M mass spectrometers using $CHCl_3$ as solvent and 3-nitrobenzyl alcohol (NBA) as matrix. The UV-Vis spectra were recorded on a Uvikon spectrophotometer using $CHCl_3$ as solvent. Elemental analyses were performed in Leco 932 and Leco 999 CHN analyzers. Column chromatography was carried out using silica gel (Merck, 35-70 mesh). Preparative thin-layer chromatography was carried out on 20 × 20 cm glass plates coated with Merck 60 silica gel (2 mm thick). Analytical TLC was carried out on precoated sheets with silica gel (Merck 60, 0.2 mm thick). 3,4-Dibromotetrahydrothiophene 1,1-dioxide was prepared in our Lab. by a colleague. *Meso*-tetrakis(2,6-dichlorophenyl)porphyrin was also prepared in our Lab. by a colleague.

3.6.2: ESI mass spectrometry study

Positive ion ESI mass spectra and tandem mass spectra were acquired using a Q-TOF 2 instrument (Micromass, Manchester, UK) using a Masslynx software system (Version 3.5). The samples for electrospray analyses were prepared by diluting 1 μL of the porphyrin solution in chloroform (~ 10^{-5} M) in 200 μL of chloroform:methanol solution (1:1, v/v)

containing 0.5% (v/v) of acetic acid. Samples were introduced into the mass spectrometer using a flow rate of 10 μL/min. Setting the needle voltage at 3000 V with the ion source at 80 ^{o}C and cone voltage at 35 V. Tandem mass spectra (MS/MS) of molecular ions were obtained using collision-induced decomposition (CID), using argon as the collision gas and varying collision energy between 40-55 eV. In MS and MS/MS experiments TOF resolution was set to approximately 9000. In MS/MS experiments Q1 resolution was set to approximately 0.7 Da.

3.6.3: 2,3-Bis(bromomethyl)-5,6-pyrazinedicarbonitrile 3.3

An ethanol (100 mL) solution of diaminomaleonitrile (0.22 g, 2 mmol) and 1,4-dibromo-2,3-butanedione (0.49 g, 2 mmol) was stirred at room temperature overnight. Ethanol was evaporated under vacuum and the residue was separated by column chromatography (silica gel) using a mixture of chloroform/light petroleum (2:1) as eluent. Compound **3.3** (0.45 g, 71% yield) was isolated as a white solid.

mp 87-89 ^{o}C (lit.[36] mp 86-87 ^{o}C).
^{1}H NMR ($CDCl_3$) δ: 4.76 (s, 4H, 2 × CH_2).

3.6.4: Attempted synthesis of pyrazine sulfone 3.5

A THF (50 mL) solution of diaminomaleonitrile (0.11 g, 1 mmol), 3,4-dibromotetrahydrothiophene 1,1-dioxide (0.28 g, 1 mmol) and potassium carbonate (0.28 g, 2 mmol) was heated at reflux for 8 hours. TLC revealed a very complicated mixture of products. Compound **3.8** (58 mg, 29% yield) was isolated as white solid by chromatography (silica gel) using a mixture of chloroform/light petroleum (1:1) as eluent.

mp 63-65 ^{o}C (lit.[20] mp 63.5-64 ^{o}C).

^{1}H NMR ($CDCl_3$) δ: 3.57 (dd, 1H, H_a, *J* 14.6 and 3.4 Hz), 3.83 (dd, 1H, H_b, *J* 14.6 and 7.7 Hz), 5.12-5.17 (m, 1H, H_c), 6.76 (dd, 1H, H_e, *J* 1.3 and 6.6 Hz), 6.85 (dd, 1H, H_d, *J* 3.1 and 6.6 Hz).

3.6.5: Diels-Alder reaction of *meso*-tetrakis(pentafluorophenyl)porphyrin with pyrazine *o*QDM

A 1,2,4-trichlorobenzene (6 mL) solution of *meso*–tetrakis(pentafluorophenyl)porphyrin **3.12a** (20 mg), 2,3-bis(bromomethyl)pyrazine **3.3** (65 mg, 10 equiv.) and sodium iodide (92 mg, 30 equiv.) was heated at reflux (214 ˚C) for 7 hours. TLC of the reaction mixture revealed the presence of unchanged starting porphyrin and four new products. The solution was diluted with $CHCl_3$ (50 mL) and washed with aqueous solution of $Na_2S_2O_3$ (3 × 10 mL) and then it was dried (Na_2SO_4). The resulting mixture was separated by column chromatography (silica gel) into three fractions using a gradient of chloroform/light petroleum as eluent. The first fraction was the unchanged starting porphyrin **3.12a** (3.5 mg, 18%). The second one was shown to be a mixture of the mono-addition compounds: a brown one **3.13a** (7.8 mg, 34% yield) and a yellow one **3.14a** (0.6 mg, 3% yield), which were then separated by preparative TLC. The third fraction was also a mixture of two compounds which after being separated by preparative TLC were identified as the bis-addition compounds: a green one **3.15a** (1.7 mg, 6% yield) and a red one **3.16a** (0.2 mg, 1% yield).

3.13a:

mp > 300 ˚C.

UV-Vis ($CHCl_3$) λ_{max} (log ε) 379 (4.71), 425 (5.32), 525 (4.20), 564 (4.20), 608 (3.97), 662 (3.95) nm.

^{1}H NMR ($CDCl_3$) δ: −2.62 (s, 2H, N*H*), 8.29 (s, 2H, quino-H), 8.76 (s, 2H, H-12 and H-13), 8.95 (d, 2H, *β*-H, *J* 5.1 Hz), 9.04 (d, 2H, *β*-H, *J* 5.1 Hz).

^{13}C NMR ($CDCl_3$) δ: 100.7, 105.7, 113.4, 123.6, 128.0, 128.5, 130.9, 134.7, 138.2, 139.1, 139.7, 145.2, 148.4, 155.7.

MS (FAB$^+$) 1127 $(M+H)^+$, 1126 $M^{+\bullet}$.

Anal. Calcd for $C_{52}H_{10}F_{20}N_8$: C, 55.43; H, 0.89; N, 9.95; Found: C, 55.13; H, 0.89; N, 10.09.

3.14a:

mp > 300 ˚C.

UV-Vis ($CHCl_3$) λ_{max} (% rel. intensity) 388 (34%), 439 (100%), 482 (35%), 651 (7%), 707 (10%) nm.

^{1}H NMR ($CDCl_3$) δ: −1.49 and −1.20 (2s, 2H, N*H*), 8.47 (s, 1H, quino-H), 8.68 (AB, 2H, H-12 and H-13, *J* 5.0 Hz), 8.79 (d, 1H, *β*-H, *J* 5.0 Hz), 8.83 (d, 1H, *β*-H, *J* 5.0 Hz), 8.94 (d, 1H, *β*-H, *J* 5.0 Hz), 9.47 (dd, 1H, *β*-H, *J* 5.0 and 11.2 Hz).

MS (FAB$^+$) 1107 $(M+H)^+$, 1106 $M^{+\bullet}$.

HRMS (FAB$^+$) Calcd for $C_{52}H_{10}F_{19}N_8$ $(M+H)^+$ 1107.0725; Found 1107.0728.

3.15a:

mp > 300 ˚C.

UV-Vis ($CHCl_3$) λ_{max} (log ε) 368 (4.70), 379 (4.70), 424 (5.28), 459 (5.17), 542 (4.20), 585 (4.79), 635 (4.21), 695 (4.47) nm.

^{1}H NMR ($CDCl_3$) δ: −2.42 (s, 2H, N*H*), 8.27 (s, 4H, quino-H), 8.96 (s, 4H, *β*-H).

MS (FAB$^+$) 1279 $(M+H)^+$, 1278 $M^{+\bullet}$.

3.16a:

mp > 300 ˚C.

UV-Vis ($CHCl_3$) λ_{max} (% rel. intensity) 379 (51%), 440 (100%), 497 (78%), 575 (23%), 676 (12%), 744 (19%) nm.

^{1}H NMR ($CDCl_3$) δ: −1.42 and −1.03 (2s, 2H, N*H*), 8.26 (s, 1H, quino-H), 8.35 (s, 1H, quino-H), 8.52 (s, 1H, quino-H), 8.72 (br d, 1H, H-8, *J* 5.0 Hz), 8.898 and 8.899 (AB, 2H, H-17 and H-18, *J* 4.8 Hz), 9.48 (ddd, 1H, H-7, *J* 1.7, 5.0 and 10.4 Hz).

MS (FAB$^+$) 1259 $(M+H)^+$, 1258 $M^{+\bullet}$.

HRMS (FAB$^+$) Calcd for $C_{60}H_{10}F_{19}N_{12}$ $(M+H)^+$ 1259.0848; Found 1259.0845.

3.6.6: Diels-Alder reaction of *meso*-tetrakis(2,6-dichlorophenyl)porphyrin with pyrazine *o*QDM

A 1,2,4-trichlorobenzene (6 mL) solution of *meso*-tetrakis(2,6-dichlorophenyl)porphyrin **3.12b** (20 mg), 2,3-bis(bromomethyl)pyrazine **3.3** (71 mg, 10 equiv.) and sodium iodide (101 mg, 30 equiv.) was heated at reflux (214 ˚C) for 7 hours. TLC of the reaction mixture revealed the presence of some unchanged starting porphyrin and four new products. The solution was diluted with $CHCl_3$ (50 mL) and washed with aqueous solution of $Na_2S_2O_3$ (3 × 10 mL) and then it was dried (Na_2SO_4). The resulting mixture was separated by column chromatography (silica gel) into three fractions using a gradient of chloroform/light petroleum as eluent. The first fraction was the unchanged starting porphyrin **3.12b** (2.2 mg, 11%). The second one was shown to be a mixture of the mono-addition compounds: a brown one **3.13b** (8.5 mg, 36% yield) and a yellow one **3.14b** (0.9 mg, 4% yield), which were then separated by preparative TLC. The third fraction was also a mixture of two compounds which after being separated by preparative TLC were identified as the bis-addition compounds: a green one **3.15b** (2.0 mg, 7% yield) and a red one **3.16b** (0.5 mg, 2% yield).

3.13b:

mp > 300 ˚C.

UV-Vis ($CHCl_3$) λ_{max} (log ε) 383 (4.72), 436 (5.46), 536 (4.23), 615 (4.02), 671 (3.72) nm.

^{1}H NMR ($CDCl_3$) δ: –2.34 (s, 2H, N*H*), 7.73-7.76 (m, 2H, Ph-H), 7.81-7.84 (m, 4H, Ph-H), 8.00 (s, 2H, quino-H), 8.02 (br s, 6H, Ph-H), 8.55 (s, 2H, H-12 and H-13), 8.75 (d, 2H, *β*-H, *J* 4.9 Hz,), 8.81 (d, 2H, *β*-H, *J* 4.9 Hz).

^{13}C NMR ($CDCl_3$) δ: 112.2, 113.9, 116.1, 123.4, 127.5, 127.6, 128.0, 129.2, 129.8, 130.9, 132.1, 133.8, 137.6, 138.4, 138.6, 138.7, 138.8, 139.1, 139.7, 145.7, 147.4, 155.1.

MS (FAB$^+$, ^{35}Cl) 1038 $(M+H)^+$.

Anal. Calcd for $C_{52}H_{22}Cl_8N_8$: C, 59.91; H, 2.13; N, 10.75; Found: C, 59.84; H, 2.14; N, 10.62.

3.14b:

mp > 300 ˚C.

UV-Vis($CHCl_3$) λ_{max} (% rel. intensity) 392 (34%), 454 (100%), 513 (26%), 681 (5%), 734 (7%) nm.

^{1}H NMR ($CDCl_3$) δ: –1.18 and –0.88 (2s, 2H, N*H*), 7.67-7.74 (m, 4H, Ph-H and quino-H), 7.92-8.12 (m, 8H, H-2^4, H-2^5 and Ph-H), 8.47 (AB, 2H, H-12 and H-13, *J* 4.9 Hz), 8.54 (d, 1H, *β*-H, *J* 4.8 Hz), 8.64 (d, 1H, *β*-H, *J* 4.8 Hz), 8.70 (d, 1H, *β*-H, *J* 4.8 Hz), 9.42 (d, 1H, *β*-H, *J* 4.8 Hz), 10.77 (dd, 1H, H-2^3, *J* 2.1 and 7.3 Hz).

^{13}C NMR (125.78 MHz, $CDCl_3$) δ: 105.4, 111.9, 113.8, 114.1, 117.1, 118.6, 121.8, 124.8, 125.5, 126.2, 127.9, 128.0, 128.1, 128.2, 128.7, 128.9, 129.0, 129.4, 129.5, 130.8, 131.6, 131.9, 132.0, 133.6, 133.7, 135.4, 136.5, 137.1, 137.7, 138.0, 138.1,138.4, 138.5, 138.7, 138.9, 139.6, 142.2, 142.7, 146.2, 149.3, 153.8, 154.5.

MS (FAB^+, ^{35}Cl) 1003 $(M+H)^+$.

HRMS (FAB^+) Calcd for $C_{52}H_{22}{}^{35}Cl_7N_8$ $(M+H)^+$ 1002.9787; Found 1002.9738.

3.15b:

mp > 300 ˚C

UV-Vis ($CHCl_3$) λ_{max} (log ε) 372 (4.73), 436 (5.39), 557 (4.39), 602 (4.68), 644 (4.29), 703 (4.36) nm.

^{1}H NMR ($CDCl_3$/TFA) δ: 8.08 (br s, 12H, Ph-H), 8.37 (s, 4H, quino-H), 8.65 (s, 4H, *β*-H).

MS (ESI, ^{35}Cl) 1191 $(M+H)^+$.

Anal. Calcd for $C_{60}H_{22}Cl_8N_{12}$: C, 60.33; H, 1.86; N, 14.07; Found: C, 60.09; H, 1.85; N, 13.88.

3.16b:

mp > 300 ˚C.

UV-Vis ($CHCl_3$) λ_{max} (% rel. intensity) 382 (40%), 456 (100%), 557 (31%), 699 (7%),767 (13%) nm.

^{1}H NMR ($CDCl_3$) δ: –1.20 and –0.82 (2s, 2H, N*H*), 7.81 (dd, 1H, Ph-H_{meta}, *J* 1.1 and 8.1 Hz), 7.94-8.14 (m, 12H, H-2^4, H-2^5 and Ph-H and quino-H), 8.22 (dd, 1H, Ph-H_{meta}, *J* 1.1 and 8.3 Hz), 8.49 (dd, 1H, *β*-H, *J* 2.0 and 5.0 Hz), 8.71 and 8.73 (AB, 2H, H-17 and H-18, *J* 5.3 Hz), 9.41 (dd, 1H, *β*-H, *J* 2.0 and 5.0 Hz), 10.80 (dd, 1H, H-2^3, *J* 2.6 and 6.9 Hz).

^{13}C NMR ($CDCl_3$) δ: 106.7, 113.2, 113.7, 113.8, 114.0, 114.4, 115.8, 122.1, 123.2, 123.4, 125.2, 125.5, 126.8, 128.5, 128.9, 129.0, 129.1, 129.2, 129.3, 129.5, 129.6, 129.7, 129.8, 131.8, 132.2, 132.3, 136.0, 136.6, 37.2, 137.6, 137.89, 137.93, 138.15, 138.21, 138.4, 138.5, 139.1, 139.45, 139.52, 139.7, 142.3, 145.16, 145.22, 146.0, 146.1, 149.6.
MS (FAB^+, ^{35}Cl) 1155 $(M+H)^+$, 1154 $M^{+\bullet}$.
HRMS (FAB^+) Calcd for $C_{60}H_{22}{}^{35}Cl_7N_{12}$ $(M+H)^+$ 1154.9910; Found 1154.9916.

3.6.7: Diels-Alder reaction of *meso*-tetraphenylporphyrin with pyrazine *o*QDM

A 1,2,4-trichlorobenzene (6 mL) solution of *meso*-tetraphenylporphyrin **3.12c** (20 mg), 2,3-bis(bromomethyl)pyrazine **3.3** (103 mg, 10 equiv.) and sodium iodide (146 mg, 30 equiv.) was heated at reflux (214 ˚C) for 7 hours. TLC of the reaction mixture revealed the presence of some unchanged starting porphyrin and four new products. The solution was diluted with $CHCl_3$ (50 mL) and washed with aqueous solution of $Na_2S_2O_3$ (3 × 10 mL) and then it was dried (Na_2SO_4). The resulting mixture was separated by column chromatography (silica gel) into three fractions using a gradient of chloroform/light petroleum as eluent. The first fraction was the unchanged starting porphyrin **3.12c** (2.7 mg, 14%). The second one was the brown compound **3.14c** (4.1 mg, 16% yield). The third fraction was the yellow compound **3.13c** (0.7 mg, 3% yield).

3.13c:
mp > 300 ˚C.
UV-Vis ($CHCl_3$) λ_{max} (% rel. intensity) 386 (19%), 439 (100%), 615 (4%) nm.
^{1}H NMR ($CDCl_3$) δ: –2.56 (s, 2H, N*H*), 7.76-7.81 (m, 8H, Ph-H and quino-H), 7.93 (t, 4H, Ph-H, *J* 7.5 Hz), 8.07 (t, 2H, Ph-H, *J* 7.5 Hz), 8.19-8.23 (m, 8H, Ph-H), 8.70 (s, 2H, H-12 and H-13), 8.86 (d, 2H, *β*-H, *J* 5.0 Hz), 8.93 (d, 2H, *β*-H, *J* 5.0 Hz).
MS (FAB^+) 767$(M+H)^+$, 766 $M^{+\bullet}$.
HRMS (FAB^+) Calcd for $C_{52}H_{31}N_8$ $(M+H)^+$ 767.2672; Found 767.2682.

3.14c:

mp > 300 ˚C.

UV-Vis($CHCl_3$) λ_{max} (log ε) 391 (4.69), 454 (5.08), 515 (4.50), 673 (3.79), 732 (3.97) nm.

^{1}H NMR ($CDCl_3$) δ: –1.76 (br s, 2H, N*H*), 7.38 (s, 1H, quino-H), 7.44 (t, 1H, H-2^4, *J* 7.9 Hz), 7.59-7.93 (m, 12H, Ph-H), 8.25-8.33 (m, 4H, H-2^5 and Ph-H), 8.47 (d, 1H, *β*-H, *J* 5.0 Hz), 8.68 (AB, 2H, H-12 and H-13, *J* 4.9 Hz), 8.71 (d, 1H, *β*-H, *J* 4.8 Hz), 8.82 (d, 1H, *β*-H, *J* 5.0 Hz), 8.94 (d, 1H, H-2^6, *J* 7.9 Hz), 9.31 (d, 1H, *β*-H, *J* 4.8 Hz), 9.35 (d, 1H, H-2^3, *J* 7.9 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ: 108.9, 113.3, 113.4, 115.9, 120.2, 122.7, 124.9, 125.5, 125.6, 126.3, 126.6, 126.9, 127.0, 127.1, 127.4, 127.8, 127.9, 128.1, 128.3, 128.55, 128.60, 129.1, 129.5, 132.7, 134.2, 134.3, 134.6, 135.2, 135.3, 136.1, 136.3, 136.5, 138.0, 139.8, 140.2, 140.6, 141.1, 141.5, 143.0, 144.1, 149.7, 153.8, 156.0.

MS (FAB^+) 765 $(M+H)^+$, 764 $M^{+\bullet}$.

Anal. Calcd for $C_{52}H_{28}N_8$: C, 81.66; H, 3.69; N 14.65; Found: C, 81.58; H, 3.64; N, 14.58.

3.6.8: Attempted formation of 3.14a from 3.13a

A 1,2,4-trichlorobenzene (4 mL) solution of porphyrin **3.13a** (8 mg) was heated at reflux (214 ˚C) for 7 hours. TLC of the reaction mixture revealed no reaction. Porphyrin **3.13a** (8 mg) was recovered by column chromatography (silica gel) using a mixture of chloroform/light petroleum (1:1) as eluent.

3.6.9: Attempted formation of 3.14b from 3.13b

A 1,2,4-trichlorobenzene (4 mL) solution of porphyrin **3.13b** (8 mg) was heated at reflux (214 ˚C) for 7 hours. TLC of the reaction mixture revealed no reaction, Porphyrin **3.14b** (8 mg) was recovered by column chromatography (silica gel) using a mixture of chloroform/light petroleum ether (1:1) as eluent.

3.6.10: Attempted formation of 3.14c from 3.13c

A 1,2,4-trichlorobenzene (2 mL) solution of porphyrin **3.13c** (1 mg) was heated at reflux (214 ˚C) for 7 hours. TLC of the reaction mixture revealed no reaction. Porphyrin **3.13c** (1 mg) was recovered by column chromatography (silica gel) using a mixture of chloroform/light petroleum (1:1) as eluent.

3.6.11: Attempted oxidative coupling of 3.13c by DDQ

A chloroform (2 mL) solution of porphyrin **3.13c** (1 mg) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (1.5 mg, 5 equiv.) was heated at reflux for 7 hours. TLC of the reaction mixture revealed no reaction. Porphyrin **3.13c** (1 mg) was recovered column chromatography (silica gel) using a mixture of chloroform/light petroleum (1:1) as eluent.

3.6.12: Diels-Alder reaction of TPP with *ortho*-benzoquinodimethane

A 1,2,4-trichlorobenzene (6 mL) solution of TPP (20 mg), α,α'-dibromo-*o*-xylene **3.17** (86 mg, 10 equiv.) and sodium iodide (146 mg, 30 equiv.) was heated at 214 ˚C for 7 hours. TLC of the reaction mixture revealed the presence of some unchanged starting porphyrin and two new products. The solution was diluted with $CHCl_3$ (50 mL) and washed with aqueous solution of $Na_2S_2O_3$ (3 × 10 mL) and then it was dried (Na_2SO_4). The residue was separated by preparative TLC. TPP (6.3 mg, 32%) was recovered. One of new products was the brown compound naphtho[2,3-*b*]porphyrin **1.28a** (0.9 mg, 4% yield). The ^1H NMR spectrum of this compound is identical with the one described in the literature.[17] The other product was the green compound **3.18** (trace amount).

1.28a:

mp > 300 ˚C.

UV-Vis($CHCl_3$) λ_{max} (% rel. intensity) 391 (13%), 418 (27%), 441 (100%), 524 (9%), 554 (3%), 605 (4%), 661 (4%) nm.

^{1}H NMR ($CDCl_3$) δ: -2.33 (s, 2H, N*H*), 7.43 (s, 2H, naphtho-H), 7.50 (dd, 2H, naphtho-H, *J* 3.1 and 6.2 Hz), 7.71 (dd, 2H, naphtho-H, *J* 3.1 and 6.2 Hz), 7.74-8.00 (m, 12H, Ph-$H_{meta,para}$), 8.20-8.23 (m, 8H, Ph-H_{ortho}), 8.65 (s, 2H, *β*-H), 8.76 (d, 2H, *β*-H, *J* 5.0 Hz), 8.86 (d, 2H, *β*-H, *J* 5.0 Hz).

MS (FAB^+) 715 $(M+H)^+$, 714 $M^{+\bullet}$.

3.18:

UV-Vis($CHCl_3$) λ_{max} (% rel. intensity) 452 (100%), 526 (12%), 562 (12%), 611 (13%), 668 (18%), 764 (8%) nm.

MS (FAB^+) 815 $(M+H)^+$, 814 $M^{+\bullet}$.

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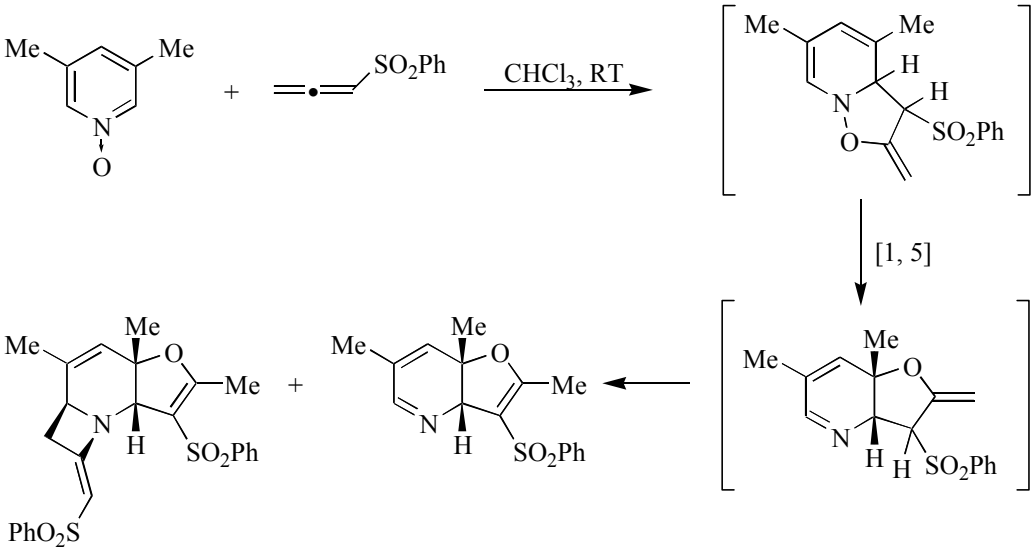
Chapter 4: 1,3-Dipolar cycloaddition reactions of porphyrinic pyridinium *N*-ylides

4.1: Pyridinium *N*-ylides − a special subclass of azomethine ylides

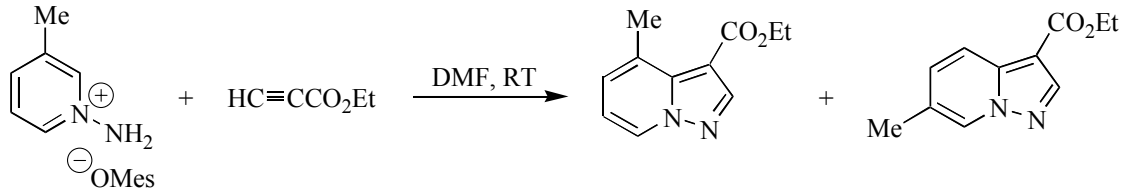
Pyridine *N*-oxides, *N*-imides and *N*-ylides show some of the reactions characteristic of 1,3-dipoles across C-2 and the exocyclic atom. Pyridinium *N*-ylides are a special subclass of azomethine ylides.

1,3-Dipolar cycloaddition reactions of pyridine *N*-oxides with unsaturated compounds have been scarcely known. They are unreactive due to a high degree of aromaticity. However, the [1,5] sigmatropic rearrangement products were obtained by way of the unstable intermediates – the cycloadducts from the cycloaddition reactions of pyridine *N*-oxides with the highly activated dipolarophiles such as isocyanates,[1] and allenes[2] (Scheme 4.1).



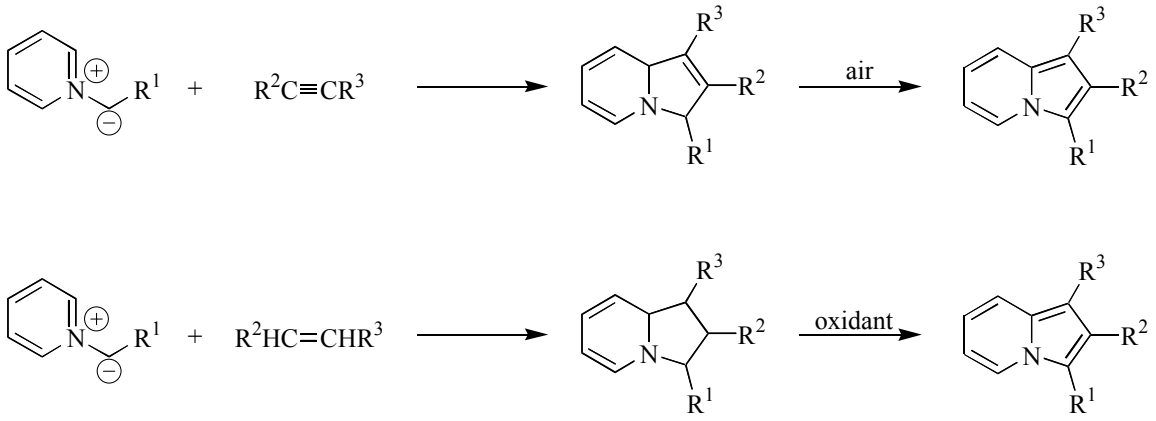
Scheme 4.1

1,3-Dipolar cycloaddition reactions of pyridine *N*-imides with activated alkynes[3] and alkenes[4] have been investigated. Ethyl 4- and 6-substituted pyrazolo[1,5-*a*]pyridine 3-carboxylates were obtained from the 1,3-dipolar cycloaddition reaction of 3-methylpyridine *N*-imide and ethyl propiolate and subsequent oxidative aromatization (Scheme 4.2).



Scheme 4.2

Synthetic indolizine derivatives are important as potential drugs,[5] spectral sensitizers,[6] and novel dyes.[7] Pyridinium *N*-ylides have been used extensively to construct indolizines because of their potentialities. The electron-deficient alkynes[8] have been used as dipolarophiles, the adducts being autoxidized by air. If alkenes replace alkynes as dipolarophiles, usually these alkenes bear a leaving group[9] or treatment with suitable oxidants such as MnO_2,[8] or tetrapyridinecobalt(II) dichromate (TPCD)[10] is necessary, since the unstable adducts can be aromatized by elimination and oxidation (Scheme 4.3). Other heteroaromatic *N*-ylides such as quinoxalinium *N*-ylides have also been reported.[11]



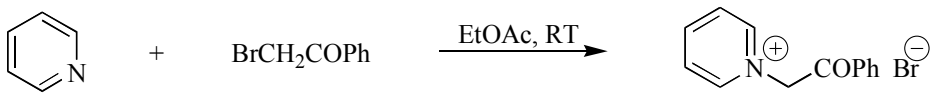
Scheme 4.3

4.2: 1,3-Dipolar cycloaddition reactions of porphyrinic pyridinium *N*-ylides

As a special subclass of azomethine ylides, pyridinium *N*-ylides show different reactivities from normal azomethine ylides. We then investigated (a) the reactivities of *meso*-tetraarylporphyrins with pyridinium *N*-ylides; (b) the cycloaddition reactions of porphyrinic pyridinium *N*-ylides.

4.2.1: Attempted formation of indolizine-fused porphyrins

The precursor of pyridinium *N*-ylide − *N*-phenacylpyridinium bromide **4.1** was prepared in 94% yield from the reaction of pyridine with one equivalent of 2-bromoacetophenone in ethyl acetate at room temperature (Scheme 4.4).[8] Since the α-H of compound **4.1** is acidic, the pyridinium *N*-ylide can be generated by the reaction of **4.1** with a base. The structure of compound **4.1** was confirmed by ^{1}H NMR. The phenyl ring protons appear as three multiplets at δ 7.51-7.57 (2H), 7.65-7.70 (1H), and 8.17-8.20 ppm (2H). The pyridyl ring protons appear as one double doublet at δ 8.07 ppm (2H, *J* 5.4 and 7.8 Hz), one triplet at δ 8.51 ppm (1H, *J* 7.8 Hz), and a doublet at δ 9.32 ppm (2H, *J* 5.4 Hz). A singlet at δ 7.22 ppm is assigned to the resonance of methylene protons.

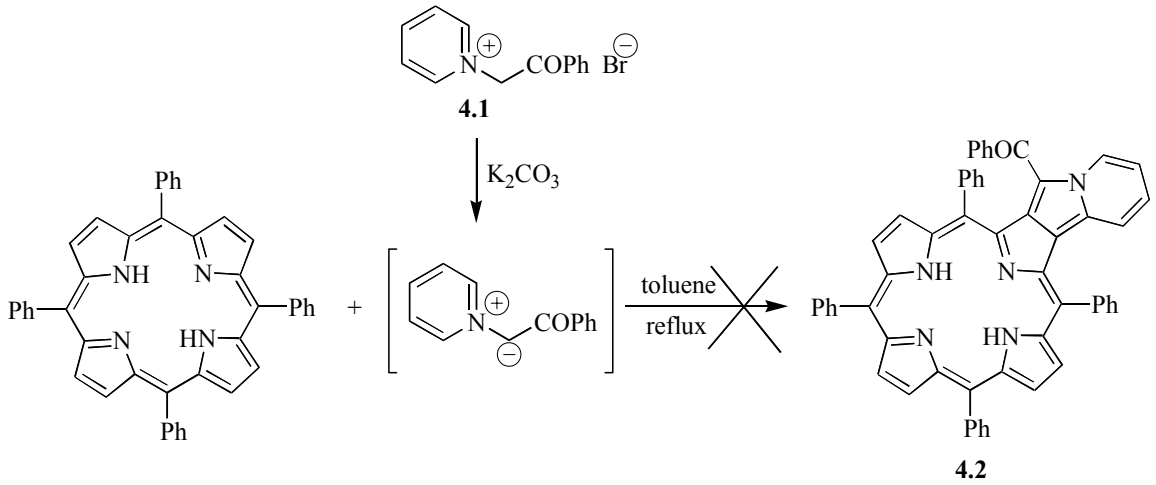


4.1

Scheme 4.4

Unfortunately, attempted formation of indolizine-fused porphyrin **4.2** from the cycloaddition reaction of TPP with pyridinium *N*-ylide generated from *N*-phenacylpyridinium bromide **4.1** in refluxing toluene failed; presumably this might be due to the difficulty of breaking the aromaticities of porphyrin and pyridine rings at same time.

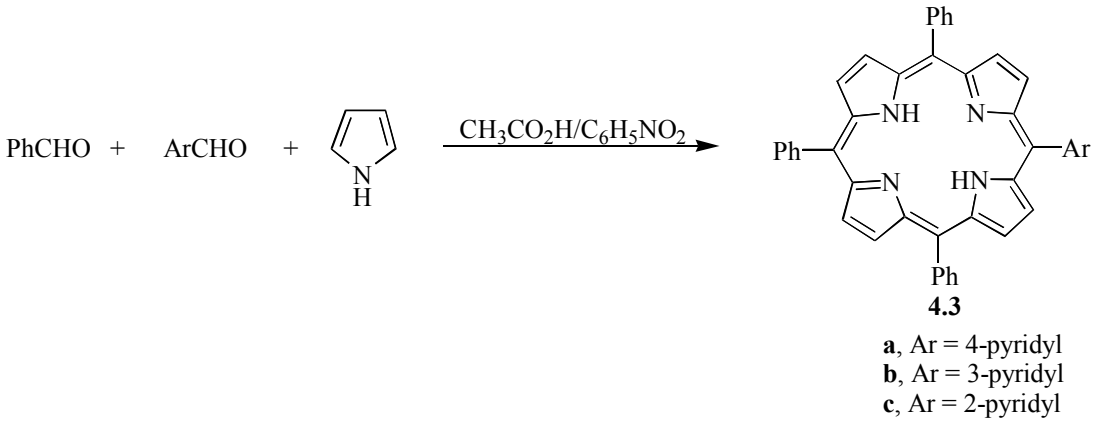
TPP (97%) was recovered (Scheme 4.5). The MnO_2-mediated cycloaddition reaction was unsuccessful too, TPP being recovered in 95%.



Scheme 4.5

4.2.2: Synthesis of pyridinium salts from *meso*-pyridylporphyrins

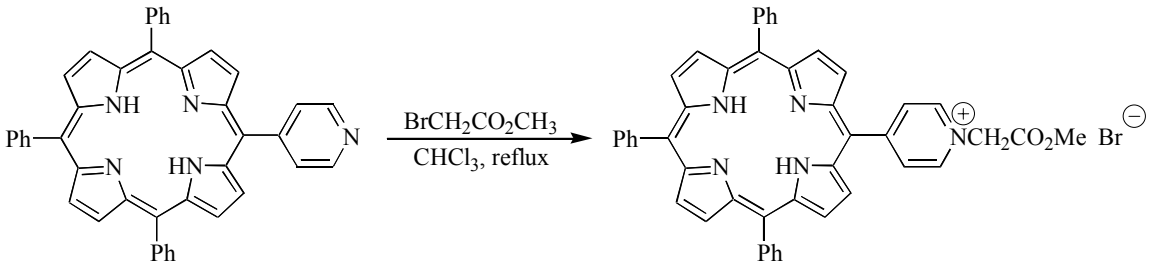
We then prepared *meso*-pyridylporphyrins **4.3** in 8-11% yields using an acid-catalyzed mixed aldehyde synthesis (Scheme 4.6). The porphyrins **4.3** can be treated as substituted pyridines for preparing the precursors of porphyrinic pyridinium *N*-ylides.



Scheme 4.6

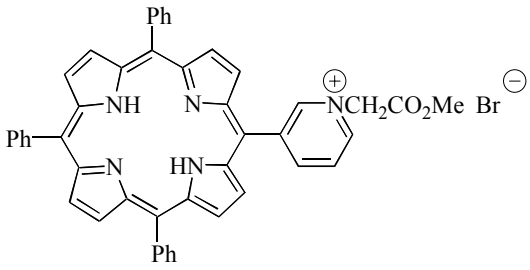
The structures of *meso*-pyridylporphyrins **4.3** were confirmed by their UV-Vis, ^{1}H NMR, and mass spectra. In the ^{1}H NMR spectrum of **4.3a**, the protons of the *meso*-phenyl groups appear as two multiplets at δ 7.72-7.78 ppm (*meta*-H and *para*-H, 9H) and δ 8.19-8.22 ppm (*ortho*-H, 6H). The eight β-pyrrolic protons appear as two doublets at δ 8.79 (2H, *J* 4.8 Hz) and 8.89 ppm (2H, *J* 4.8 Hz) and an AB spin system at δ 8.86 ppm (4H, *J* 5.1 Hz). The pyridyl ring protons appear as an AA´BB´ spin system at δ 8.16 (2H, *J* 1.6 and 4.4 Hz) and δ 9.01 ppm (2H, *J* 1.6 and 4.4 Hz). The FAB mass spectrum of **4.3a** shows intense peaks at *m/z* 616 ($[M+H]^+$) and 615 ($[M]^{+\bullet}$) while its UV-Vis spectrum is similar to that of TPP (λ_{max} 417, 514, 549, 588, 645 nm).

The porphyrinic pyridinium salt **4.4a** was synthesized in 93% yield from the reaction of porphyrin **4.3a** and 5 equivalents of methyl bromoacetate in refluxing chloroform for 80 hours (Scheme 4.7). The pyridinium salts **4.4b** was synthesized in 96% yield in the same way. Unfortunately, after refluxing a chloroform solution of porphyrin **4.3c** with methyl bromoacetate for 80 hours, TLC revealed that most starting porphyrin was unchanged and this is probably due to the steric hindrance effect. Porphyrin **4.3c** (93%) was recovered and porphyrin **4.4c** was not obtained.

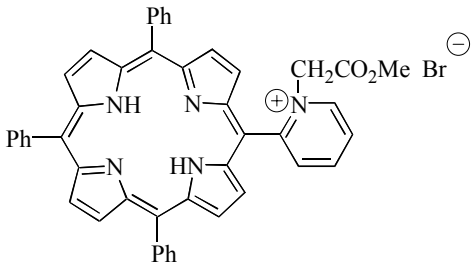


4.3a **4.4a**

Scheme 4.7



4.4b

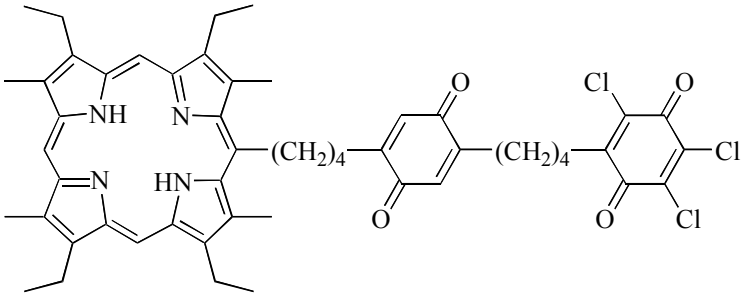


4.4c

The structures of the new compounds were confirmed by their UV-Vis, ^{1}H NMR, and mass spectra. In the ^{1}H NMR spectrum of **4.4a**, the methyl ester group protons appear as the singlet at δ 3.91 ppm, the methylene protons appear as another singlet at δ 6.78 ppm. The protons of the *meso*-phenyl groups appear as two multiplets at δ 7.73-7.82 (*meta*-H and *para*-H, 9H) and δ 8.16-8.21 ppm (*ortho*-H, 6H). The doublet at δ 8.98 ppm (2H, *J* 4.8 Hz) corresponds to two β-pyrrolic protons and the multiplet at δ 8.80-8.89 ppm (8H) corresponds to other six β-pyrrolic protons and two pyridyl ring protons are observed. The other two pyridyl ring protons appear as a doublet at δ 9.76 ppm (2H, *J* 6.7 Hz). The pyridyl ring protons were shifted to downfield when compared with those in **4.3a**. The FAB mass spectrum of **4.4a** shows intense peaks at *m/z* 688 ($[M-Br]^+$), while its UV-Vis spectrum shows Soret and Q bands at 417, 520, 570, 654 nm.

4.2.3: Cycloaddition reactions of porphyrins 4.4a,b with quinones

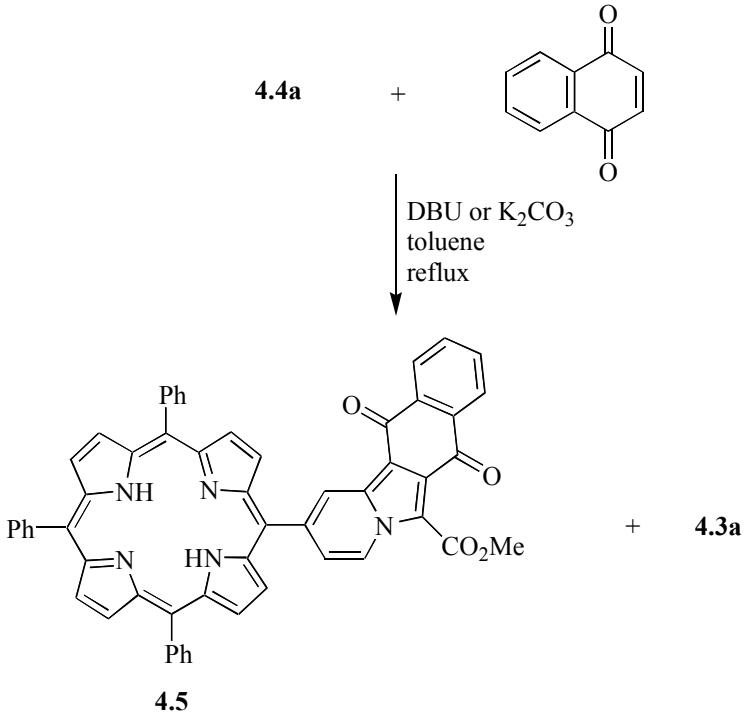
Electron transfer (ET) reactions in biological systems provide one of the most fascinating fields of current interdisciplinary research. Photosynthetic reaction centers (RC) consist of the protein matrix and the donor-acceptor redox active pigments. In RC, photo-induced electron transfer (PET) takes place within about 3 ps after singlet excitation and initial energy conversion act proceeds with a quantum yield of nearly unity. The unpaired electron moves energetically downhill from (bacterio)chlorophylls or their corresponding dimers to bacteriopheophytins and quinone acceptors.[12] Although the natural system is complicated, those simple synthetic models still give us some informations with regard to the reaction mechanism and structural features of important components. To gain a better insight into the dependencies of PET rate constants on donor-acceptor distance, relative orientation, free energy of reaction, and electronic coupling, various covalent linked porphyrin-quinone with different bridging features have been designed and studied for this purpose.[13] On the other hand, some porphyrin-quinone compounds have also shown potential as anticancer agents,[14] and others can be used as nonlinear optical (NLO) materials,[15] fluorescent chemosensors[16] and catalysts.[17]



Porphyrin-diquinone triad for PET study

Recently, our group has synthesized some porphyrin-quinone model systems *via* Diels-Alder reactions[18] or 1,3-dipolar cycloaddition reactions.[19] We then tried the 1,3-dipolar cycloaddition reactions of porphyrins **4.4a,b** with quinones (1,4-benzoquinone and 1,4-naphthoquinone). In these reactions, excess of quinones were used both as dipolarophiles and oxidants.

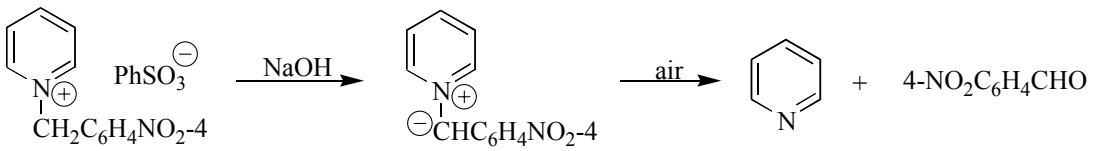
The cycloadditions of porphyrin **4.4a** with 1,4-naphthoquinone were carried out in refluxing toluene, and different bases (DBU and potassium carbonate) have been used to generate the pyridinium *N*-ylides from porphyrin **4.4a** (Scheme 4.8). Porphyrin-quinone compound **4.5** was obtained with DBU or K_2CO_3 (16% yield with DBU, 4% yield with K_2CO_3).



Scheme 4.8

The ^{1}H and ^{13}C NMR and mass spectra of the new compound and its elemental analysis confirm the expected structure – porphyrin-quinone **4.5**. In the ^{1}H NMR spectrum of **4.5**, the methyl ester group protons appear as a singlet at δ 4.24 ppm. The three protons at the pyridyl ring appear as three double doublets at δ 8.10 (*J* 1.9 and 7.3 Hz), 9.52 (*J* 0.9 and 1.9 Hz) and 9.70 ppm (*J* 0.9 and 7.3 Hz). The eight β-pyrrolic protons appear as an AB spin system at 8.87 ppm (2H, *J* 4.8 Hz) and two doublets at δ 8.91 (2H, *J* 4.9 Hz) and δ 8.95 ppm (2H, *J* 4.9 Hz). A multiplet at δ 7.72-7.80 ppm corresponding to *meta*-H and *para*-H of *meso*-phenyl group and two naphthoquinone-H (11H), another multiplet at δ 8.21-8.24 ppm corresponding to *ortho*-H of *meso*-phenyl group and one naphthoquinone-H (7H), and the third multiplet at δ 8.31-8.34 ppm corresponding to one naphthoquinone-H are observed. The ^{13}C NMR spectrum of compound **4.5** shows the signals corresponding to the three carbonyl groups at δ 162.1 ppm (ester group) and at δ 179.7 and 180.5 ppm (quinone). The FAB mass spectrum of **4.5** shows intense peaks at *m/z* 842 ($[M+H]^{+}$) and 841 ($[M]^{+\bullet}$), while its UV-Vis spectrum shows Soret and Q bands at 421, 517, 556, 591, 648 nm, similar to those from **4.3a**.

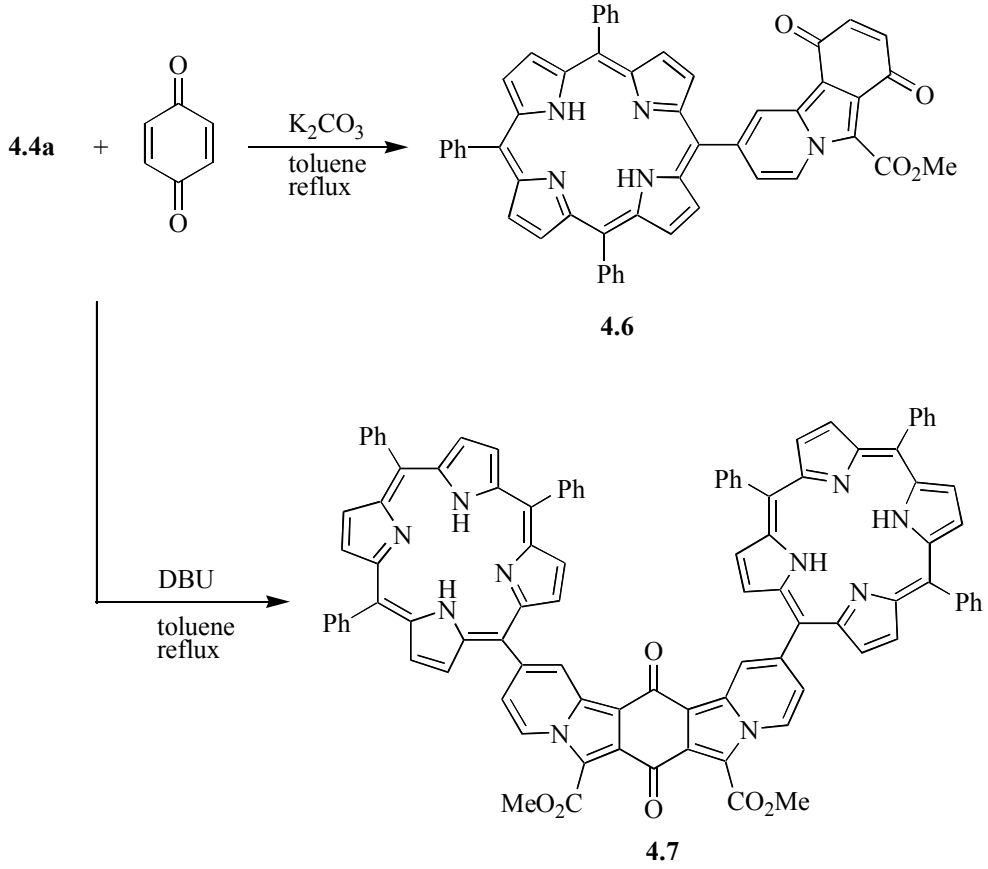
The by-product of these cycloaddition reactions is the dealkylation compound **4.3a** (16% yield with DBU and 82% yield with K_2CO_3). To confirm this, we refluxed compound **4.4a** in the presence of DBU or K_2CO_3 (in the absence of any dipolarophile) and in fact it was converted into **4.3a** (61% yield with DBU; 59% yield with K_2CO_3). The carbon-nitrogen bond cleavage in pyridinium compounds is not surprising, since it has been shown in the literature that it corresponds to the oxidation of the carbanion by oxygen (Scheme 4.9).[20]



Scheme 4.9

The 1,3-dipolar cycloaddition product formed in the reactions of porphyrins **4.4a** with 1,4-benzoquinone is highly dependent on the base being used (Scheme 4.10). When potassium carbonate was used, the mono-addition compound **4.6** was obtained in 11% yield. However, with DBU, bis-addition occurred and a novel porphyrinic dimer **4.7** was

obtained in 16% yield. In both cases, the porphyrin **4.3a** was also isolated (32% yield with K_2CO_3 and 19% yield with DBU).

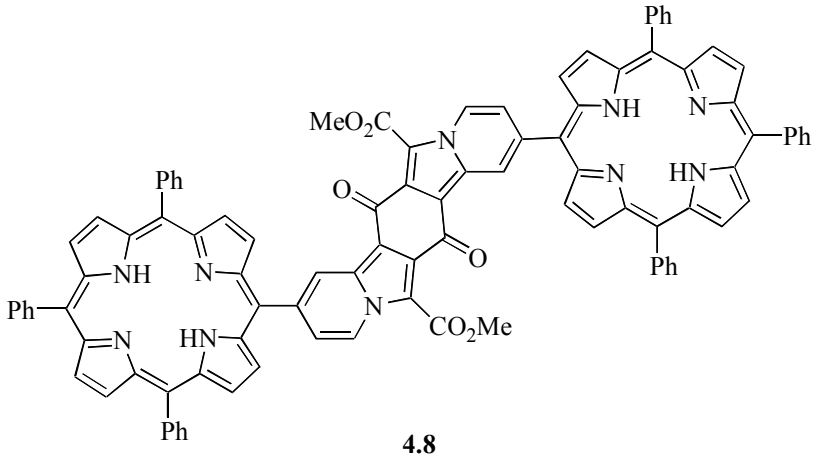


Scheme 4.10

The structures of **4.6** and **4.7** were deduced from their UV-Vis, ^{1}H, ^{13}C NMR, mass spectra. Their UV-Vis spectra are similar to the one of **4.3a**. In ^{1}H NMR spectrum of **4.6**, a singlet at δ 4.18 ppm, corresponding to the methyl ester group, and an AB system at δ 6.81 and 6.83 ppm (*J* 10.3 Hz) corresponding to the two protons of the quinone moiety are observed. The three protons at the pyridyl ring appear as three double doublets at δ 8.05 (*J* 1.9 and 7.3 Hz), 9.29 (*J* 0.9 and 1.9 Hz) and 9.71 ppm (*J* 0.9 and 7.3 Hz), while the protons of *meso*-phenyl groups appear as two multiplets at δ 7.74-7.80 (*meta* and *para*-H, 9H) and δ 8.21-8.24 ppm (*ortho*-H, 6H). The eight β-pyrrolic protons appear as two AB spin systems at δ 8.86 (4H, *J* 4.8 Hz) and 8.90 ppm (4H, *J* 4.8 Hz). The ^{13}C NMR spectrum of compound **4.6** shows the signals corresponding to the three carbonyl groups at δ 161.8 ppm (ester group) and at δ 181.3 and 182.1 ppm (quinone). The FAB mass spectrum shows

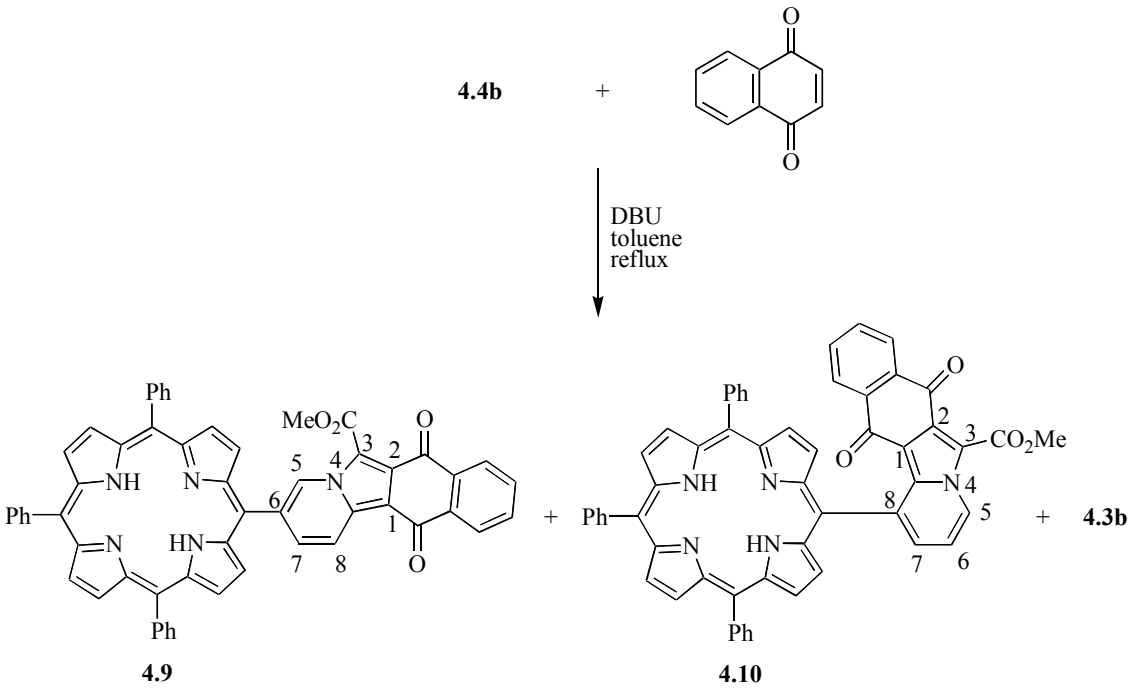
peaks at *m/z* 793 and 794 which are two units higher than the expected. Our explanation of this observation is that the quinone, under FAB conditions, is reduced and the observed peaks correspond to $[M+3H]^+$ (794) and to $[M+2H]^{+\bullet}$ 793 (see Chapter 3).

When we compare the ^1H NMR spectrum of **4.7** with the one of compound **4.6**, the main difference is the absence of the signals corresponding to the protons of the quinone moiety. This is a clear evidence that a bis-addition occurred. The mass spectrum shows intense peaks at *m/z* 1475 ($[M+H]^+$) and 1474 ($[M]^{+\bullet}$), confirming that it is in fact a bis-addition product. The addition of a second porphyrinic *N*-ylide to compound **4.6**, followed by aromatization, could lead to compound **4.7** or to its isomer **4.8**. However, only one of them was isolated. The ^{13}C NMR spectrum of the compound shows three signals corresponding to carbonyl groups: one at δ 162.2 ppm corresponding to the ester group, and the other two at δ 177.5 and 177.9 ppm corresponding to the two carbonyl groups of quinone ring. This spectrum fits only with structure **4.7**, since structure **4.8** has only two non-equivalent carbonyl groups. The explanation of the fact that a mono-addition product is formed when potassium carbonate is used and a bis-addition compound is formed in the presence of DBU is probably related to the fact that in the first case we have a two-phase reaction while with DBU it is a homogenous reaction.



4.8

The reaction of the *meta*-isomer **4.4b** with 1,4-naphthoquinone afforded two regioisomeric compounds **4.9** (10% yield) and **4.10** (5% yield), the major one being **4.9** (Scheme 4.11), which is probably due to the steric hindrance effect. In this reaction we also get the non-alkylated pyridyl porphyrin **4.3b** (28% yield).



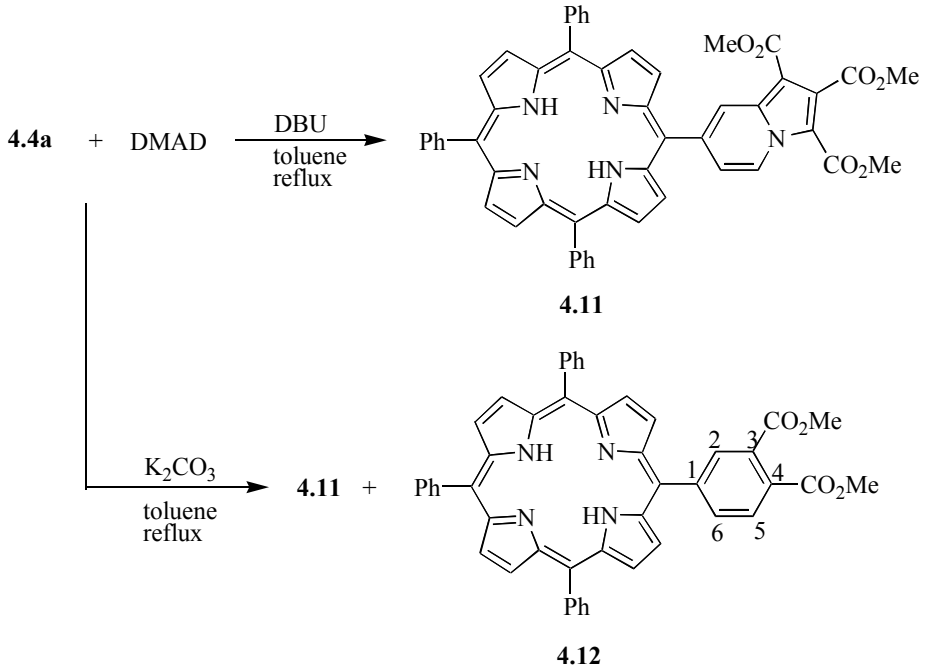
Scheme 4.11

The structures of two new compounds were deduced from their UV-Vis, ^{1}H NMR and mass spectra. Both mass spectra show intense peaks at *m/z* 842 ($[M+H]^+$) and 841 ($[M]^{+\bullet}$), confirming the two expected porphyrin-quinones **4.9** and **4.10**. The two isomers show very similar UV-Vis spectra with the one of **4.3a**; the two isomers were distinguished from each other by ^{1}H and COSY NMR spectra. The proton H_5 at pyridyl ring of **4.9** appears as a broad singlet at δ 10.13 ppm due to the small long-range coupling, while the proton H_6 of **4.10** appears as a triplet at δ 7.48 ppm (*J* 7.1 Hz). The other two protons at the pyridyl ring in both cases appear as double doublets.

4.2.4: Cycloaddition reactions of porphyrin 4.4a with dimethyl acetylenedicarboxylate (DMAD)

The 1,3-dipolar cycloaddition reactions of porphyrin **4.4a** with the electron-deficient alkyne, dimethyl acetylenedicarboxylate (DMAD), were carried out in refluxing toluene (Scheme 4.12). When DBU was used as base, TLC revealed a main product and various

compounds in small amounts. The expected 1,3-dipolar cycloaddition compound **4.11** was obtained in 39% yield as the main product. The dealkylated porphyrin **4.3a** was also isolated in 2% yield from the reaction mixture. When the reaction was carried out in the presence of potassium carbonate, TLC revealed two main products and various compounds in small amounts. Together with the expected 1,3-dipolar cycloaddition compound **4.11** in 20% yield, porphyrin **4.12** was also formed in 17% yield.

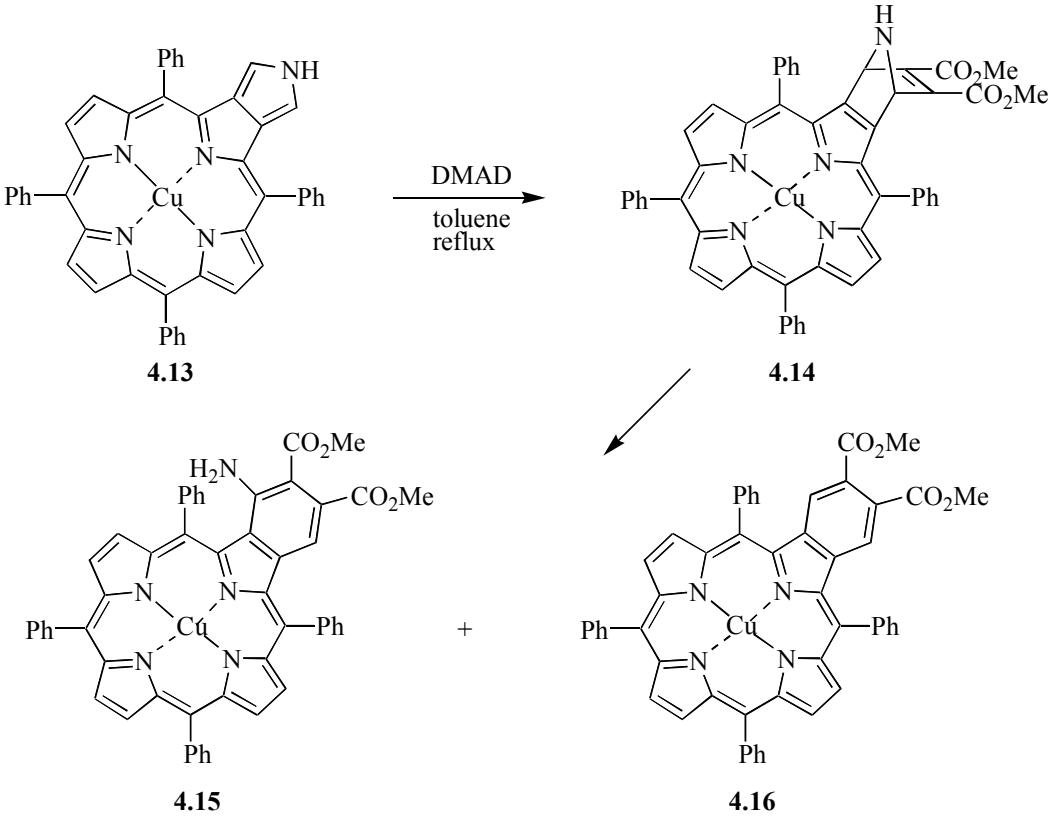


Scheme 4.12

The structures of the new compounds **4.11** and **4.12** were characterized by their UV-Vis, ^{1}H, ^{13}C NMR and mass spectra. The mass spectrum of compound **4.11** shows intense peaks at *m/z* 828 ($[M+H]^{+}$) and 827 ($[M]^{+\bullet}$), confirming that it is a 1,3-dipolar cycloaddition reaction product. Its ^{1}H NMR shows, in the aliphatic region, the protons of three methyl ester groups appearing as three singlets at δ 3.80, 4.05 and 4.11 ppm. In the aromatic region, the three protons of the pyridyl ring appear as three double doublets at δ 8.00 (*J* 1.9 and 7.2 Hz), 9.14 (*J* 0.9 and 1.9 Hz) and 9.87 ppm (*J* 0.9 and 7.2 Hz). The ^{13}C NMR spectrum of the compound shows three signals at δ 160.7, 163.4 and 166.3 ppm corresponding to three carbonyl ester groups. However, the mass spectrum of compound **4.12** shows intense peaks at *m/z* 731 ($[M+H]^{+}$) and 730 ($[M]^{+\bullet}$), suggesting that it is a Diels-Alder reaction compound. Its ^{1}H NMR shows only two singlets at δ 3.98 and 4.11

ppm corresponding to the resonances of two methyl ester group. The proton H_2 appears as doublet at δ 8.59 ppm (*J* 1.7 Hz), the proton H_5 appears as a doublet at δ 8.14 ppm (*J* 7.9 Hz), the proton H_6 appears as double doublet at δ 8.40 ppm (*J* 1.7 and 7.9 Hz). Chemical shifts are at highfield when compared with those of the pyridyl protons in compound **4.11**, indicating it is a phenyl ring not a pyridyl ring. The ^{13}C NMR spectrum of **4.12** shows two signals at δ 168.1 and 168.3 ppm corresponding to carbonyl groups. All this is consistent with structure **4.12**, as a Diels-Alder reaction product.

In fact, it is not surprising to obtain porphyrin **4.12** from the Diels-Alder reaction of porphyrin **4.4a** with dimethyl acetylenedicarboxylate (DMAD). Smith *et al.* have reported that porphyrin derivative **4.14** was formed from the Diels-Alder reaction of pyrrolo[3,4-*b*]porphyrin **4.13** with DMAD (Scheme 4.13). Upon prolonged heating in refluxing toluene, derivative **4.14** was converted into benzoporphyrins **4.15** and **4.16**, finally, **4.16** was the sole product.[21]



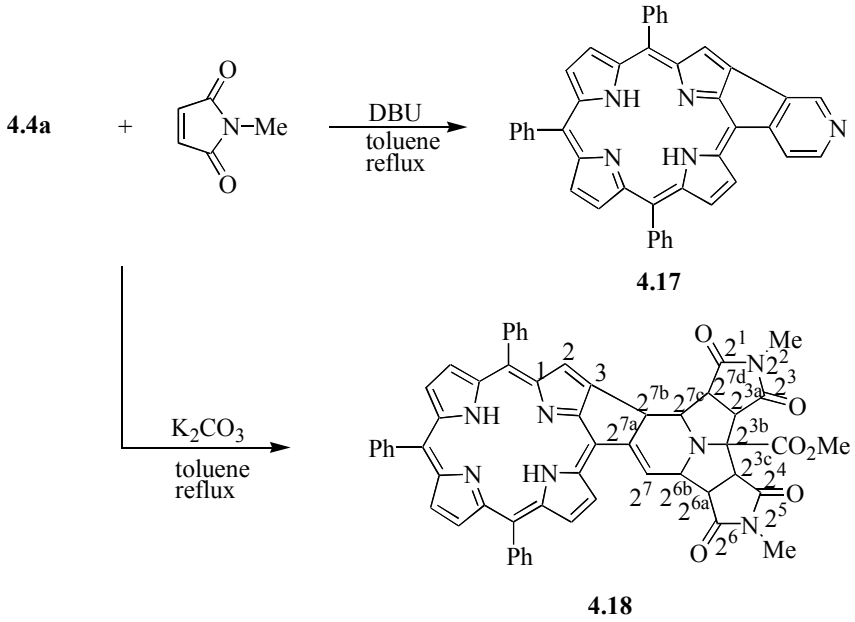
Scheme 4.13

4.2.5: Reactions of porphyrin 4.4a with electron-deficient alkenes

Usually the adducts of pyridinium *N*-ylides with electron-deficient alkenes are not stable. But, in some cases, the primary adducts were isolated,[22] and in other cases, some products were obtained.[22b] We therefore investigated the reactions of porphyrin **4.4a** with the following electron-deficient alkenes: *N*-methyl maleimide, dimethyl fumarate, dimethyl maleate, in refluxing toluene, without oxidants such as tetrapyridinecobalt(II) dichromate (TPCD).

4.2.5.1: Reactions of porphyrin 4.4a with *N*-methyl maleimide

The product formed in the reactions of porphyrin **4.4a** with *N*-methyl maleimide is also highly dependent on the base used. A novel *meso*+β fused porphyrin **4.17** was isolated in 31% yield when DBU was used. The dealkylated porphyrin **4.3a** was also isolated in 14% yield. However, with potassium carbonate, porphyrin **4.18** was isolated in 14% yield from a complicated mixture (other porphyrins in trace amounts). TLC showed that there was no dealkylated porphyrin **4.3a** (Scheme 4.14).



Scheme 4.14

The structures of the new compounds were full characterized by their NMR [1D: ^{1}H, ^{13}C, and DEPT 135; 2D: COSY, NOESY, HSQC and HMBC], mass and UV-Vis spectroscopic techniques.

It is very clear from the ^{1}H and ^{13}C NMR spectra of **4.17** that there are no sp^3 carbons (and the corresponding protons) ruling out the possibility of *N*-methyl maleimide moiety being incorporated in this product. In the ^{1}H NMR (Fig. 4.1-4.2), the two NH protons appear as two singlets at δ -0.34 and 1.22 ppm. The three protons at the pyridyl ring appear as one broad doublet at δ 7.63 ppm (*J* 4.8 Hz), one doublet at δ 8.16 ppm (*J* 4.8 Hz) and one broad singlet at δ 8.28 ppm. The six β-pyrrolic protons appear as two doublets at δ 8.24 and 8.29 ppm (*J* 4.7 Hz), and four double doublets at 8.33 (*J* 1.9 and 4.7 Hz), 8.38 (*J* 1.8 and 4.7 Hz), 8.58 (*J* 1.4 and 5.0 Hz) and 8.86 ppm (*J* 1.2 and 5.0 Hz) due to the long-range coupling with inner NH. The other β-pyrrolic proton H-2 and the *meta*-H and *para*-H of the *meso*-phenyl groups appear as a multiplet at δ 7.67-7.74 ppm (10H). The *ortho*-H of the *meso*-phenyl groups appear as a multiplet at δ 8.00-8.03 ppm (6H). Its FAB mass spectrum shows intense peaks at *m/z* 614 ($[M+H]^+$) and 613 ($[M]^{+\bullet}$), 2 Da less than **4.3a**, confirming it is *meso*+β fused porphyrin **4.17**. Its UV-Vis spectrum shows a pronounced red shift of both Soret and Q bands (λ_{max} 446, 470, 495, 637, 741 nm) relative to **4.3a** (Fig. 4.3), confirming that it is a porphyrin with an extended π system. In this case, the splitting of Soret band is also observed.

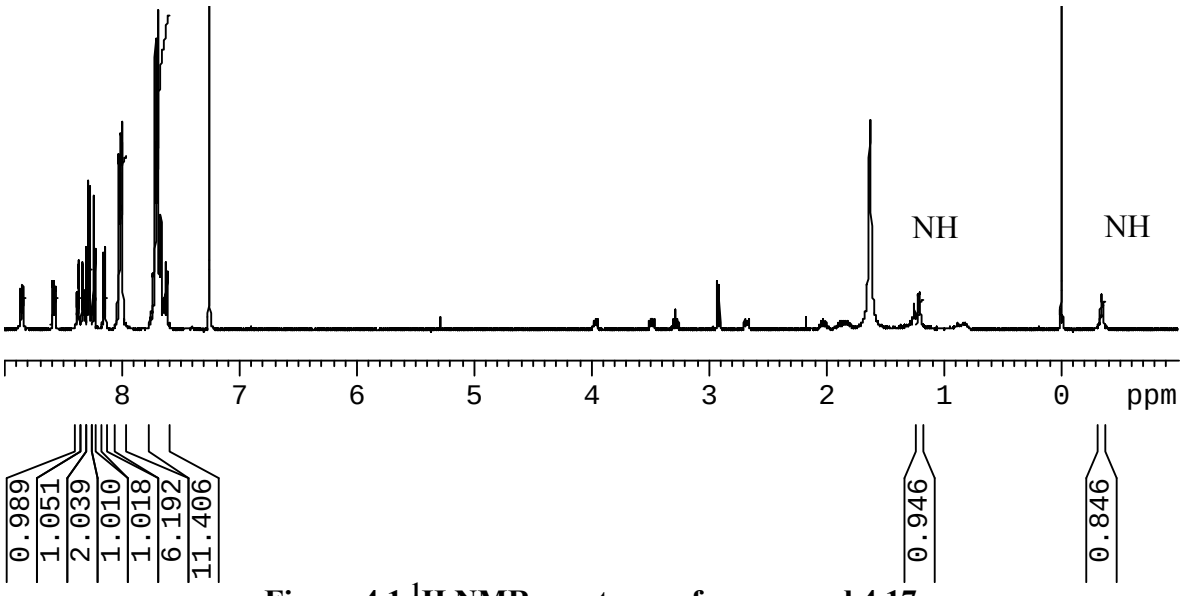


Figure 4.1 ^{1}H NMR spectrum of compound 4.17

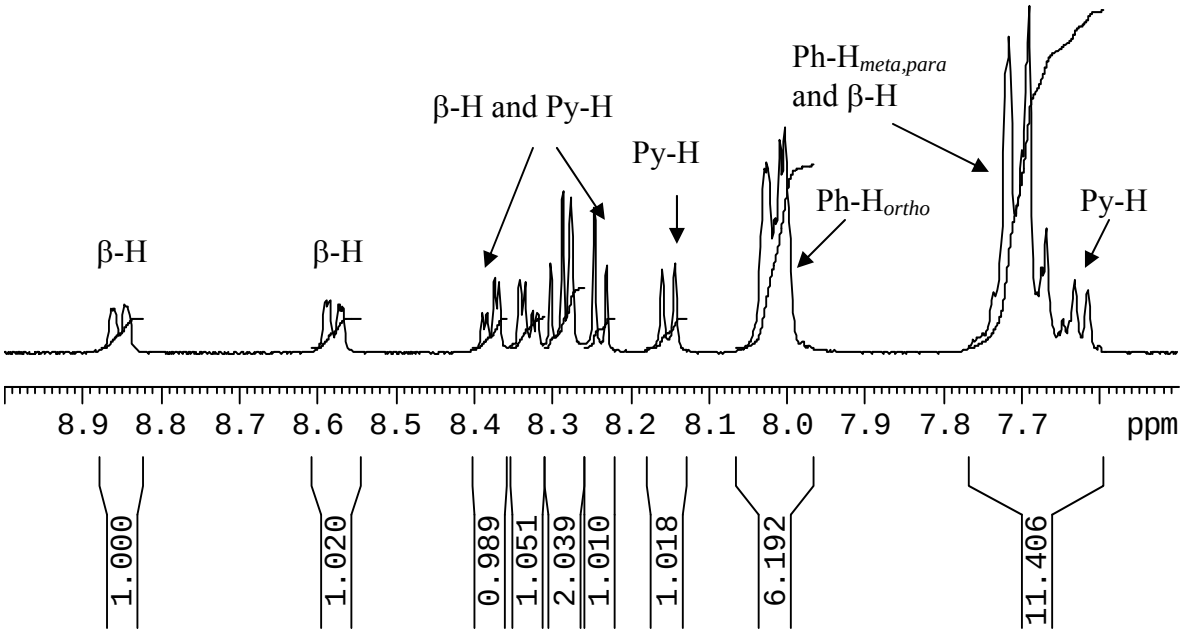


Figure 4.2 ^{1}H NMR spectrum of compound 4.17 (aromatic region)

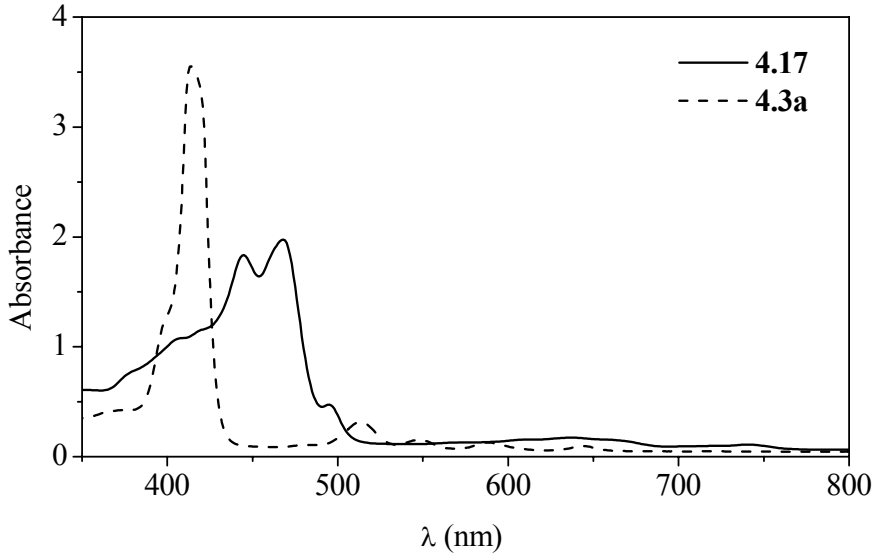


Figure 4.3 UV-Vis spectra of porphyrins 4.3a and 4.17

The FAB mass spectrum of compound **4.18** shows intense peaks at *m/z* 908 ($[M+H]^{+}$) and 907 ($[M]^{+\bullet}$), which means it is a molecule incorporated by one *N*-ylide and two *N*-

methyl maleimide moieties. In ^{1}H NMR (Fig. 4.4-4.6), two NH protons appear as two singlets at δ –2.52 and –1.55 ppm, since the fused ring is not an aromatic ring, NH protons appear at highfield. The protons of the *meso*-phenyl groups are detected as two multiplets at δ 7.71-7.81 (*meta*-H and *para*-H, 9H) and 8.11-8.30 ppm (*ortho*-H, 6H). Besides H-2 at δ 8.81 ppm (doublet, *J* 1.7 Hz), the other six β-pyrrolic protons appear as four doublets at δ 8.68 (*J* 4.7 Hz), 8.73 (*J* 4.7 Hz), 9.05 (*J* 4.8 Hz) and 9.63 ppm (*J* 4.8 Hz), and two double doublets at δ 8.83 (1.8 and 4.9 Hz) and 8.90 ppm (*J* 1.5 and 4.9 Hz) due to long-range coupling with inner NH. For those aliphatic protons, the important couplings observed in the COSY NMR are presented in Figure 4.7, the important NOE found in the NOESY NMR are shown in Figure 4.8. The COSY and NOESY NMR spectra are particularly important for the assignment for the structure **4.18**. Its UV-Vis spectrum shows a little red shift of both Soret and Q bands (λ_{max} 430, 533, 572, 600, 654 nm) relative to **4.3a**, since the porphyrin core conjugates with a double bond not with an aromatic ring. The ^{13}C NMR spectrum shows signals due to nine sp^3 carbons and five carbonyl carbons. The DEPT 135 spectrum confirms that there is only one aliphatic quaternary carbon (C-2[3b]). Therefore, the structure **4.18** is established by the full NMR study, UV-Vis and mass spectra.

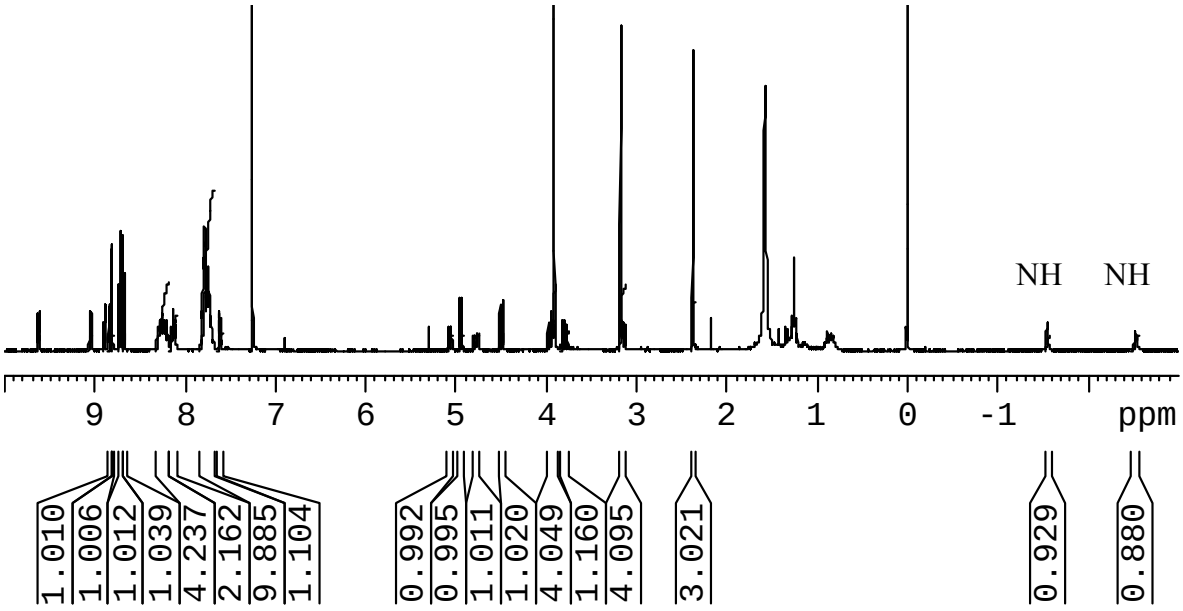


Figure 4.4 ^{1}H NMR spectrum of compound 4.18

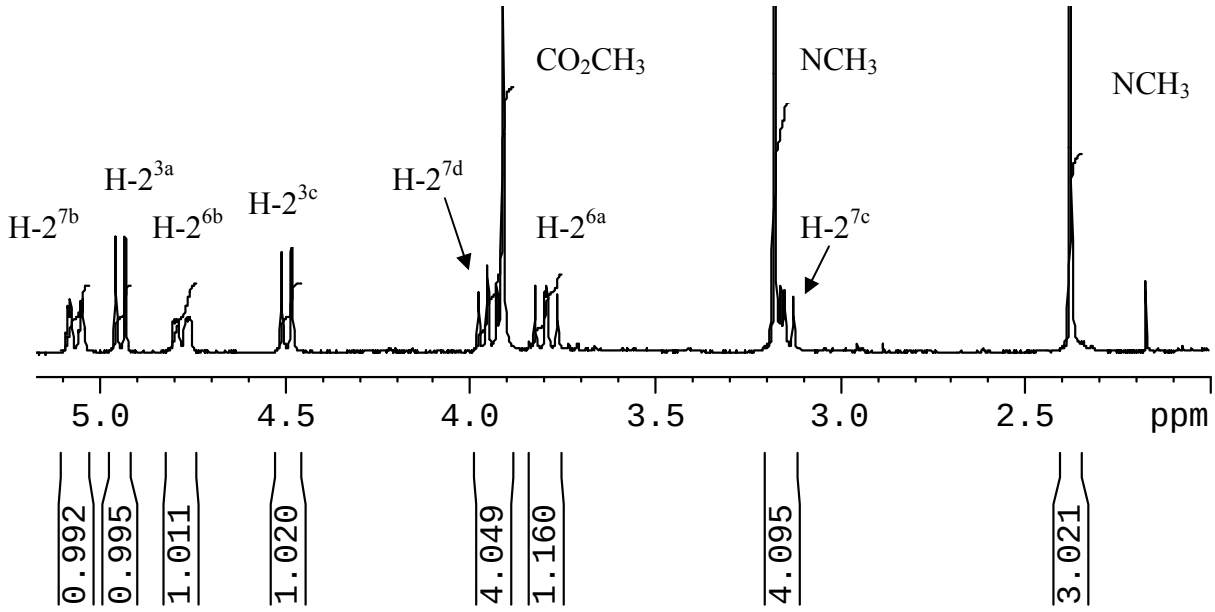


Figure 4.5 ^{1}H NMR spectrum of compound 4.18 (aliphatic region)

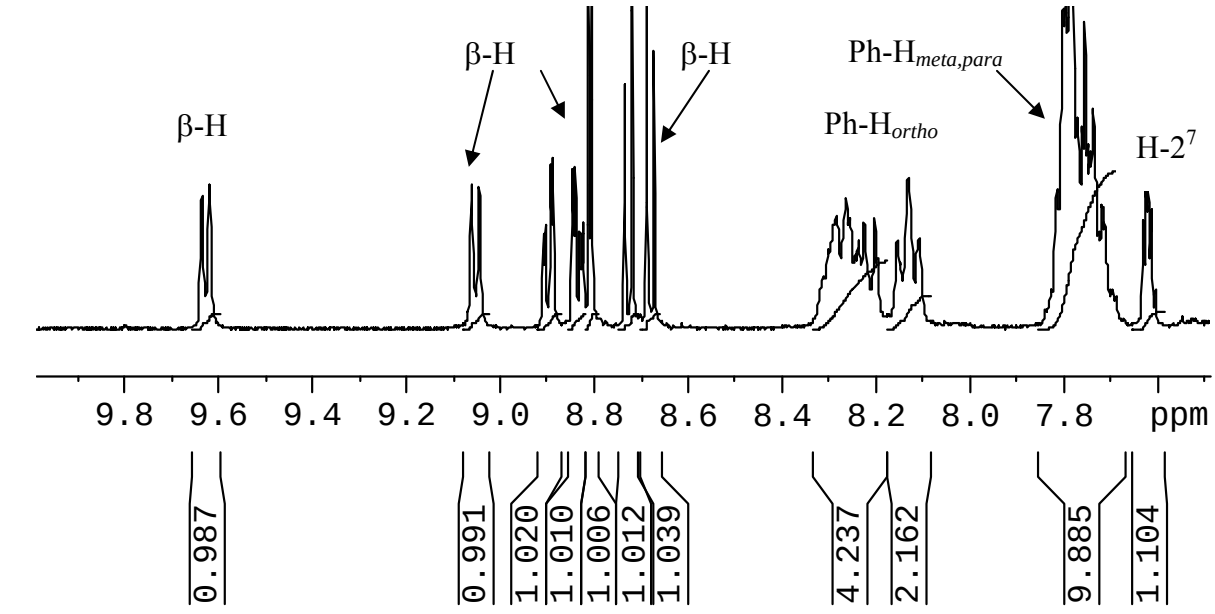


Figure 4.6 ^{1}H NMR spectrum of compound 4.18 (aromatic region)

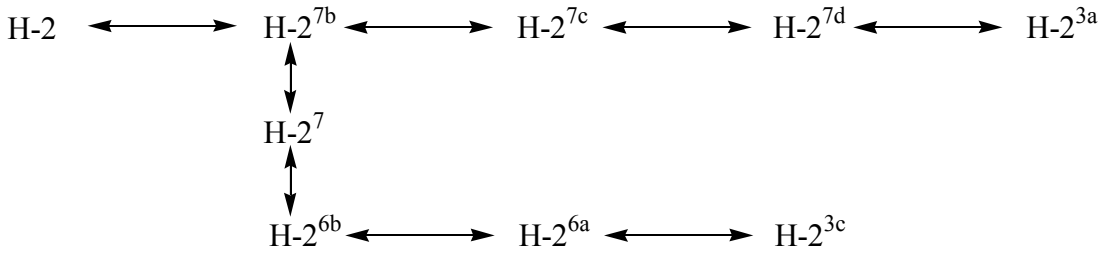


Figure 4.7 Important couplings observed in the COSY spectrum of compound 4.18

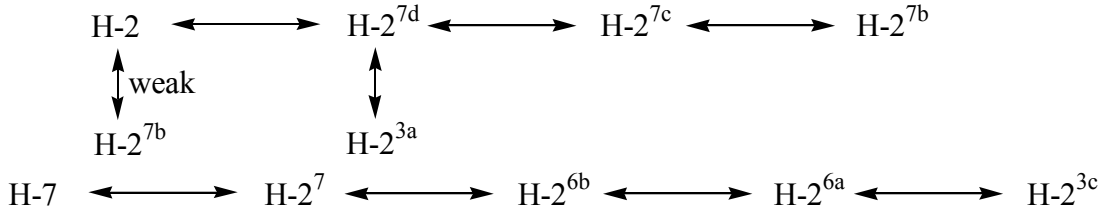
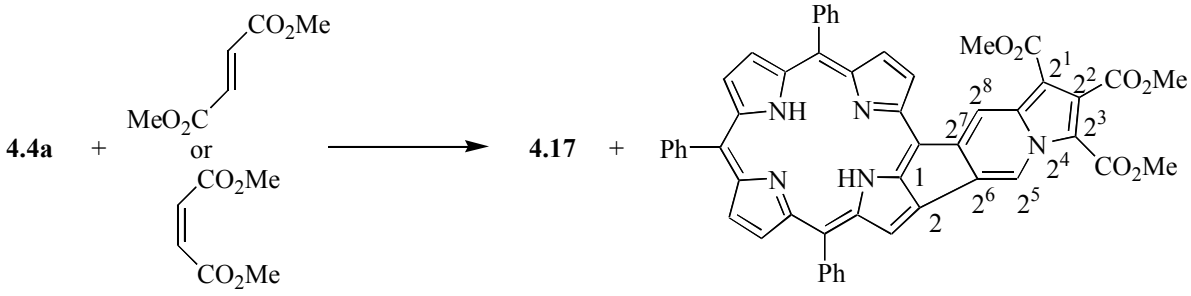


Figure 4.8 Important NOE observed in the NOESY spectrum of compound 4.18

4.2.5.2: Reactions of porphyrin 4.4a with dimethyl fumarate or dimethyl maleate

The reactions of porphyrin **4.4a** with dimethyl fumarate or dimethyl maleate gave complex mixtures (Scheme 4.15). In both cases, DBU was used as base; together with porphyrin **4.17** (6% yield with dimethyl fumarate, 34% yield with dimethyl maleate), the porphyrin **4.19** was also obtained (4% yield with dimethyl fumarate, 2% yield with dimethyl maleate). The porphyrin **4.19** resulted from the expected [3+2] cycloaddition and fusion of the modified group with the neighbouring beta position of the macrocycle.



Scheme 4.15

The structure of the new compound was deduced from its UV-Vis, ^{1}H NMR and mass spectra. In the ^{1}H NMR spectrum of compound **4.19**, it is the same situation with other *meso*+β fused π-extended porphyrins, two NH protons shift to downfield and show two singlets at δ 1.01 and 0.27 ppm, while the NH protons of compound **4.11** without *meso*+β fusion appear as singlet at δ -2.76 ppm. In contrast to compound **4.17**, there are three singlets at δ 3.96, 4.04 and 4.11 ppm corresponding to the resonances of three methyl ester groups in the spectrum of **4.19**, which indicates it is a [3+2] cycloaddition compound. But in the aromatic region, only seven β-pyrrolic protons are observed, appearing as one AB spin system at δ 8.43 ppm (2H, *J* 4.8 Hz), two doublets at δ 8.83 (*J* 5.0 Hz) and 9.42 ppm (*J* 5.0 Hz), two double doublets at δ 8.54 (*J* 1.8 and 4.8 Hz) and 8.63 ppm (*J* 1.4 and 4.8 Hz), due to the long-range coupling with inner NH, and one singlet at δ 9.48 ppm (H-3) which is confirmed by NOESY studies. Also different from compound **4.11**, only two protons are observed at the pyridyl ring, which appear as two singlets at δ 8.18 (H-2^5) and 9.13 ppm (H-2^8).The FAB mass spectrum shows intense peaks at *m/z* 826 ($[M+H]^+$) and 825 ($[M]^{+\bullet}$), confirming that it is an oxidative coupling compound from **4.11**. Its UV-Vis spectrum shows a pronounced red shift of both Soret and Q bands (λ_{max} 376, 422, 476, 512, 587, 636, 711 nm) relative to **4.11** (λ_{max} 417, 516, 553, 590, 646 nm) (Fig. 4.9), confirming it is a porphyrin **4.19** with an extended π system. A shoulder of the Soret band is observed.

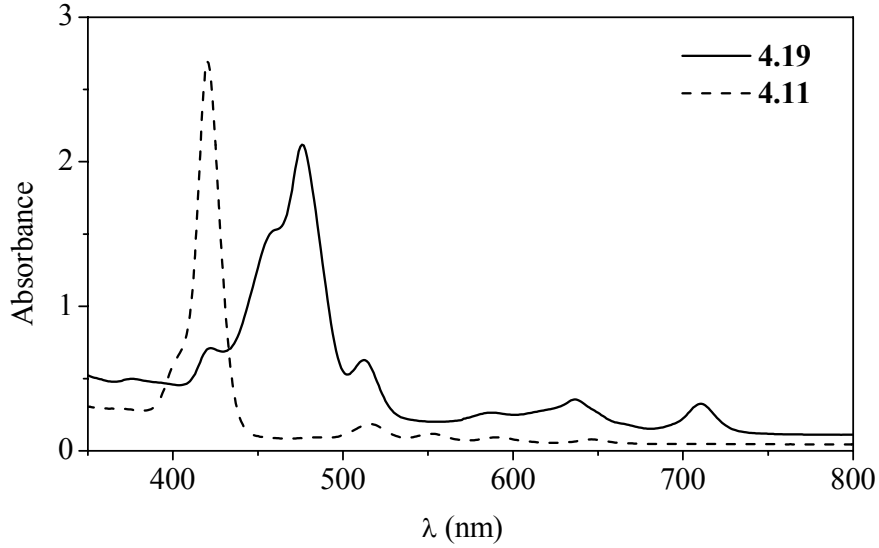
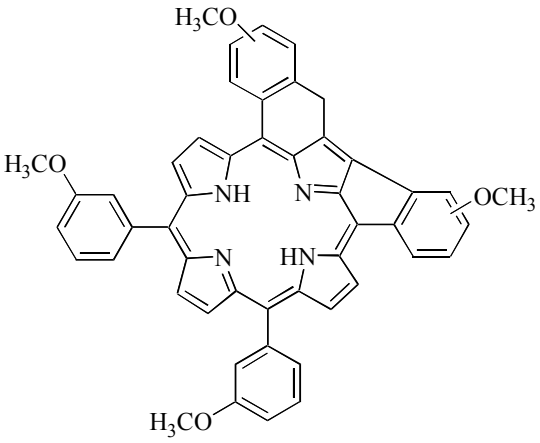
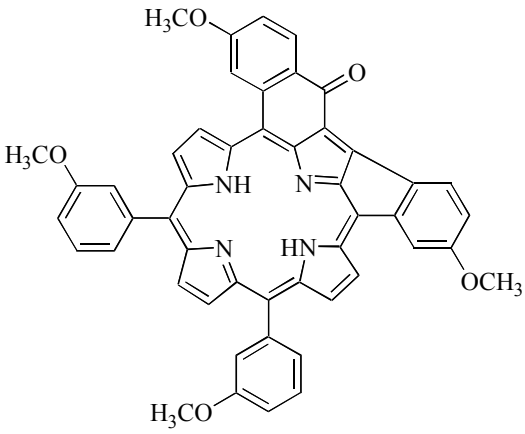


Figure 4.9 UV-Vis spectra of porphyrins 4.11 and 4.19

Dolphin *et al.* reported that the *meso*+β fused porphyrins **4.20**, **4.21** and either **4.22** or **4.23** were isolated from the cyclization reaction of β-formyl-*meso*-tetrakis(3-methoxylphenyl)porphyrin.[23] Callot *et al.* also isolated the same type of compound from the amination of porphyrin **2.20**.[24] The *meso*+β fused porphyrins such as **4.24** have also been synthesized from the intramolecular Pd(0) catalyzed couplings on *ortho*-iodinated *meso*-phenyl porphyrins.[25] These fused rings are five-membered and result from a cyclization process involving the *ortho*-position of the *meso*-phenyl ring and the adjacent β-position. The present work shows for the first time a cyclization process involving the *ortho*-position of the *meso*-pyridyl ring and the adjacent β-position. In terms of mechanism this might parallel the mechanism proposed by Dolphin *et al.* for such cyclization process through carbonium ion intermediates.[23]



4.20



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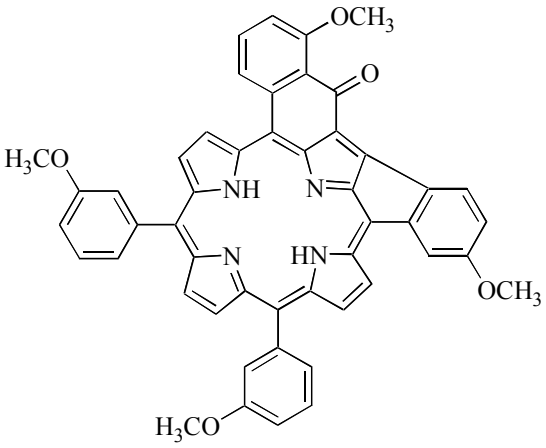
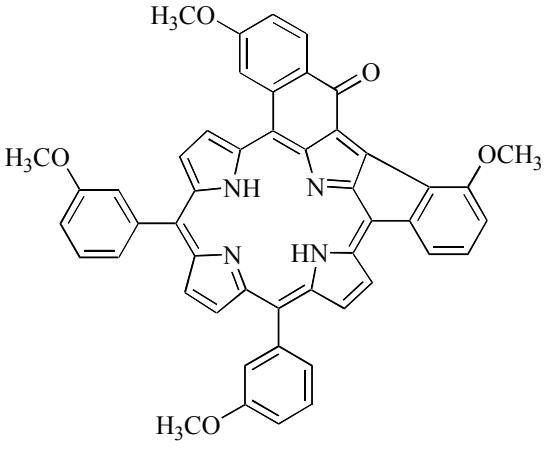
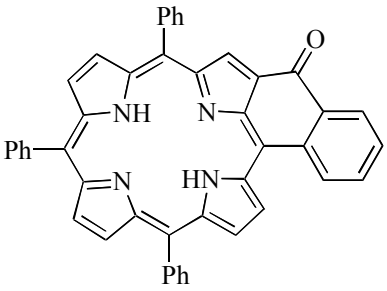


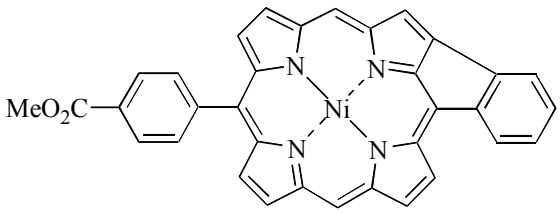
4.22



4.23



2.20



4.24

4.3: Conclusion

Reactions of porphyrinic pyridinium *N*-ylides **4.4a,b** with quinones have been studied. In these reactions, excess of quinones were used both as dipolarophiles and oxidants, and novel porphyrin-quinone dyads (triad) were obtained. The product formed in the reactions of porphyrins **4.4a** with 1,4-benzoquinone is highly dependent on the base used. When potassium carbonate was used, the mono-addition compound **4.6** was obtained. However, with DBU, bis-addition occurred and a novel porphyrinic dimer **4.7** was isolated. Such porphyrin-quinone dyads (triad) can be used in further studies trying to understand the photosynthetic electron-transfer mechanism.

The product formed in reactions of porphyrin **4.4a** with electron-deficient alkyne – dimethyl acetylenedicarboxylate (DMAD), is also highly dependent on the base used. With DBU, the [3+2] cycloaddition reaction product **4.11** was obtained. The [4+2] cycloaddition reaction product **4.12** was also isolated together with **4.11** when potassium carbonate was used as base.

Novel π-extended polycyclic products were obtained from a cyclization process involving the *ortho*-position of the pyridine ring and the adjacent β-position when porphyrin **4.4a** reacted with electron-deficient alkenes, *N*-methyl maleimide, dimethyl fumarate, or dimethyl maleate (without oxidant TPCD). With different bases (DBU and potassium carbonate), different results were obtained. Such π-extended porphyrins have potential biomedical or materials applications due to the absorption at the far red end of the visible spectrum.

4.4: Experimental Section

4.4.1: General

Melting points were measured on a Reichert Thermovar apparatus fitted with a microscope and are uncorrected. ^{1}H, and ^{13}C NMR spectra were recorded on a Bruker Avance 300 spectrometer at 300.13 and 75.47 MHz, respectively. $CDCl_3$ was used as solvent and TMS as internal reference; the chemical shifts are expressed in δ (ppm) and the coupling constants (*J*) in Hertz [Hz]. Unequivocal ^{1}H assignments were made with aid of 2D COSY ($^{1}H/^{1}H$) and NOESY spectra (mixing time of 800 ms), while ^{13}C assignments were made on the basis of 2D HSQC and HMBC (delays for long-range *J* C/H couplings were optimized for 7 Hz) experiments. FAB Mass spectra and HRMS spectra were recorded on VG AutoSpec Q and M mass spectrometers using $CHCl_3$ as solvent and 3-nitrobenzyl alcohol (NBA) as matrix (thioglycerol as matrix for cationic porphyrins). ESI HRMS spectrum was recorded on APEX III FT-ICR mass spectrometer. The UV-Vis spectra were recorded on a Uvikon spectrophotometer using $CHCl_3$ as solvent. Elemental analyses were performed in Leco 932 and Leco 999 CHN analyzers. Column chromatography was carried out using silica gel (Merck, 35-70 mesh). Preparative thin-layer chromatography was carried out on 20 × 20 cm glass plates coated with Merck 60 silica gel (2 mm thick). Analytical TLC was carried out on precoated sheets with silica gel (Merck 60, 0.2 mm thick).

4.4.2: Synthesis of *N*-phenacylpyridinium bromide 4.1[8]

A mixture of pyridine (0.81 mL, 10 mmol) and 2-bromoacetophenone (1.99 g, 10 mmol) in ethyl acetate (20 mL) was stirred at room temperature overnight. The precipitated solid was collected and rinsed with ethyl acetate (20 mL) to give *N*-phenacylpyridinium bromide **4.1** (2.61 g, 94% yield) as a white solid.

mp 200-202 °C (lit.[26] mp 194.5-197 °C).

^{1}H NMR ($CDCl_3$) 7.22 (s, 2H, CH_2), 7.51-7.57 (m, 2H, Ph-H), 7.65-7.70 (m, 1H, Ph-H), 8.07 (dd, 2H, Py-H, *J* 5.4 and 7.8 Hz), 8.17-8.20 (m, 2H, Ph-H), 8.51 (t, 1H, Py-H, *J* 7.8 Hz), 9.32 (d, 2H, Py-H, *J* 5.4 Hz).

4.4.3: Attempted formation of indolizine-fused porphyrin 4.2

A toluene (5 mL) solution of TPP (20 mg), *N*-phenacylpyridinium bromide **4.1** (45 mg, 5 equiv.) and potassium carbonate (27 mg, 6 equiv.) was heated at reflux for 12 hours. TLC of the reaction mixture revealed that TPP was unchanged. After removal of solvent under vacuum, the residue was separated by column (silica gel) with chloroform/light petroleum as eluent (1:1). TPP was recovered (19.4 mg, 97%).

4.4.4: 5-(4´-Pyridyl)-5,10,15-triphenylporphyrin 4.3a[27]

A solution of 4-pyridine carboxaldehyde (0.89 mL, 9.3 mmol) and benzaldehyde (2.21 mL, 21.6 mmol) in glacial acetic acid (210 mL) and nitrobenzene (150 mL) was heated at 120 °C. Pyrrole (2 mL, 28.8 mmol) was added within 15 minutes. The temperature was maintained at 120 °C for 45 minutes. The solution was cooled down to room temperature and kept overnight. The solvents were distilled under vacuum. The residue was washed with light petroleum (3 × 20 mL) and separated by column chromatography (silica gel) using chloroform as eluent. The unsymmetrical *meso*-pyridylporphyrins **4.3a** (0.47 g, 11% yield) was isolated from the statistical mixture of products.

UV-Vis ($CHCl_3$) λ_{max} (% rel. intensity) 417 (100%), 514 (6%), 549 (3%), 588 (3%), 645 (2%) nm.

^{1}H NMR ($CDCl_3$) -2.81 (s, 2H, N*H*), 7.72-7.78 (m, 9H, Ph-H$_{meta,para}$), 8.16 (AA´BB´, 2H, Py-H, *J* 1.6 and 4.4 Hz), 8.19-8.22 (m, 6H, Ph-H$_{ortho}$), 8.79 (d, 2H, β-H, *J* 4.8 Hz), 8.86

(AB, 4H, β-H, *J* 5.1 Hz), 8.89 (d, 2H, β-H, *J* 4.8 Hz), 9.01 (AA´BB´, 2H, Py-H, *J* 1.6 and 4.4 Hz).
MS (FAB$^+$) 616 $(M+H)^+$, 615 $M^{+\bullet}$.

4.4.5: 5-(3´-Pyridyl)-5,10,15-triphenylporphyrin 4.3b[28]

A solution of 3-pyridine carboxaldehyde (0.88 mL, 9.3 mmol) and benzaldehyde (2.21 mL, 21.6 mmol) in glacial acetic acid (210 mL) and nitrobenzene (150 mL) was heated at 120 ^oC. Pyrrole (2 mL, 28.8 mmol) was added within 15 minutes. The temperature was maintained at 120 ^oC for 45 minutes. The solution was cooled down to room temperature and kept overnight. The solvents were distilled under vacuum. The residue was washed with light petroleum (3 × 20 mL) and separated by column chromatography (silica gel) using chloroform as eluent. The unsymmetrical *meso*-pyridylporphyrins **4.3b** (0.48 g, 11% yield) was isolated from the statistical mixture of products.

UV-Vis ($CHCl_3$) λ_{max} (% rel. intensity) 415 (100%), 514 (8%), 549 (4%), 589 (3%), 644 (3%) nm.
^{1}H NMR ($CDCl_3$) -2.80 (s, 2H, N*H*), 7.73-7.82 (m, 10H, Py-H and Ph-$H_{meta,para}$), 8.21-8.23 (m, 6H, Ph-H_{ortho}), 8.53 (dt, 1H, Py-H, *J* 1.9 and 7.7 Hz), 8.79 (d, 2H, β-H, *J* 4.8 Hz), 8.86 (AB, 4H, β-H, *J* 4.8 Hz), 8.90 (d, 2H, β-H, *J* 4.8 Hz), 9.04 (dd, 1H, Py-H, *J* 1.4 and 4.9 Hz), 9.46 (d, 1H, Py-H, *J* 1.9 Hz).
MS (FAB$^+$) 616 $(M+H)^+$, 615 $M^{+\bullet}$.

4.4.6: 5-(2´-Pyridyl)-5,10,15-triphenylporphyrin 4.3c[29]

A solution of 2-pyridine carboxaldehyde (0.89 mL, 9.3 mmol) and benzaldehyde (2.21 mL, 21.6 mmol) in glacial acetic acid (210 mL) and nitrobenzene (150 mL) was heated at 120 ^oC. Pyrrole (2 mL, 28.8 mmol) was added within 15 minutes. The temperature was

maintained at 120 ^{o}C for 45 minutes. The solution was cooled down to room temperature and kept overnight. The solvents were distilled under vacuum. The residue was washed with light petroleum (3 × 20 mL) and separated by column chromatography (silica gel) using chloroform as eluent. The unsymmetrical *meso*-pyridylporphyrins **4.3c** (0.36 g, 8% yield) was isolated from the statistical mixture of products.

UV-Vis ($CHCl_3$) λ_{max} (% rel. intensity) 414 (100%), 514 (14%), 549 (6%), 589 (5%), 644 (3%) nm.
^{1}H NMR ($CDCl_3$) -2.79 (s, 2H, N*H*), 7.70-7.79 (m, 10H, Py-H and Ph-H$_{meta,para}$), 8.11 (dt, 1H, Py-H, *J* 1.8 and 7.7 Hz), 8.20-8.23 (m, 6H, Ph-H$_{ortho}$), 8.26 (dt, 1H, Py-H, *J* 1.0 and 7.7 Hz), 8.82-8.85 (m, 6H, β-H), 8.88 (d, 2H, β-H, *J* 4.9 Hz), 9.14 (ddd, 1H, Py-H, *J* 1.0, 1.8 and 4.9 Hz).
MS (FAB$^+$) 616 $(M+H)^+$, 615 $M^{+\bullet}$.

4.4.7: Synthesis of pyridinium salt 4.4a

A chloroform (50 mL) solution of porphyrin **4.3a** (100 mg) and methyl bromoacetate (0.08 mL, 5 equiv.) was heated at reflux for 80 hours. TLC of the reaction mixture revealed that the starting porphyrin was consumed. The solution was concentrated and then precipitated by light petroleum (50 mL). Porphyrin **4.4a** (116 mg, 93% yield) was filtered off, washed with light petroleum and then dried under vacuum.

mp > 300 ºC.
UV-Vis ($CHCl_3$) λ_{max}/nm (log ε) 417 (5.12), 520 (4.05), 570 (4.01), 654 (3.80).
^{1}H NMR ($CDCl_3$) -2.72 (s, 2H, N*H*), 3.91 (s, 3H, CO_2CH_3), 6.78 (s, 2H, CH_2), 7.73-7.82 (m, 9H, Ph-H$_{meta,para}$), 8.16-8.21 (m, 6H, Ph-H$_{ortho}$), 8.80-8.89 (m, 8H, β-H and Py-H), 8.98 (d, 2H, β-H, *J* 4.8 Hz), 9.76 (d, 2H, Py-H, *J* 6.7 Hz).
^{13}C NMR ($CDCl_3$) 53.9 (CO_2CH_3), 60.8 (CH_2), 110.8, 121.8, 123.0, 126.9, 128.1, 131.9, 132.8, 133.3, 134.5, 141.4, 141.5, 144.3, 161.2, 166.9 (CO_2CH_3).
MS (FAB$^+$) 688 $(M-Br)^+$.

4.4.8: Synthesis of pyridinium salt 4.4b

A chloroform (50 mL) solution of porphyrin **4.3b** (100 mg) and methyl bromoacetate (0.08 mL, 5 equiv.) was heated at reflux for 80 hours. TLC of the reaction mixture revealed that the starting porphyrin was consumed. The solution was concentrated and then precipitated by light petroleum (50 mL). Porphyrin **4.4b** (120 mg, 96% yield) was filtered off, washed with light petroleum and then dried under vacuum.

mp > 300 ºC.
UV-Vis ($CHCl_3$) λ_{max}/nm (log ε) 422 (5.29), 519 (4.21), 555 (3.81), 591 (3.77), 647 (3.61).
^{1}H NMR ($CDCl_3$) -2.82 (s, 2H, N*H*), 3.89 (s, 3H, CO_2CH_3), 6.60 (s, 2H, CH_2), 7.72-7.82 (m, 9H, Ph-$H_{meta,para}$), 8.09-8.21 (m, 6H, Ph-H_{ortho}), 8.31 (dd, 1H, Py-H, *J* 6.4 and 7.9 Hz), 8.82-8.86 (m, 6H, *β*-H), 8.97 (d, 2H, *β*-H, *J* 4.8 Hz), 9.01 (d, 1H, Py-H, *J* 7.9 Hz), 9.50 (br s, 1H, Py-H), 10.24 (d, 1H, Py-H, *J* 6.4 Hz).
^{13}C NMR ($CDCl_3$) 53.9 (CO_2CH_3), 61.6 (CH_2), 108.1, 121.4, 122.3, 125.9, 126.8, 128.0, 134.5, 141.4, 141.6, 142.8, 146.0, 147.5, 149.1, 166.8 (CO_2CH_3).
MS (FAB^+) 688 $(M\text{-}Br)^+$.

4.4.9: Attempted synthesis of pyridinium salt 4.4c

A chloroform (50 mL) solution of porphyrin **4.3c** (100 mg) and methyl bromoacetate (0.08 mL, 5 equiv.) was heated at reflux for 80 hours. TLC of the reaction mixture revealed that almost all the porphyrin **4.3c** was unchanged. The solvent was distilled under vacuum. The residue was separated by column chromatography (silica gel) using chloroform as eluent. The starting porphyrin **4.3c** (93.3 mg, 93% yield) was recovered.

4.4.10: Synthesis of porphyrin-quinone 4.5 using DBU as base

A toluene (6 mL) solution of pyridinium salt **4.4a** (20 mg), 1,4-naphthoquinone (82 mg, 20 equiv.) and DBU (0.19 mL) was refluxed for 8 hours. TLC of the reaction mixture revealed the presence of two new products. The solvent was distilled under vacuum. The residue was separated by column chromatography (silica gel) using chloroform as eluent. The first fraction isolated was the porphyrin-quinone **4.5** (3.5 mg, 16% yield). The second fraction isolated was the dealkylated compound **4.3a** (2.6 mg, 16% yield).

mp > 300 ºC.

UV-Vis ($CHCl_3$) λ_{max} (log ε) 421 (5.54), 517 (4.33), 556 (4.10), 591 (3.84), 648 (3.73) nm.

^{1}H NMR ($CDCl_3$) -2.75 (s, 2H, N*H*), 4.24 (s, 3H, CO_2CH_3), 7.72-7.80 (m, 11H, naphthoquinone-H and Ph-$H_{meta,para}$), 8.10 (dd, 1H, indolizine-H, *J* 1.9 and 7.3 Hz), 8.21-8.24 (m, 7H, naphthoquinone-H and Ph-H_{ortho}), 8.31-8.34 (m, 1H, naphthoquinone-H), 8.87 (AB, 4H, *β*-H, *J* 4.8 Hz), 8.91 (d, 2H, *β*-H, *J* 4.9 Hz), 8.95 (d, 2H, *β*-H, *J* 4.9 Hz), 9.52 (dd, 1H, indolizine-H, *J* 0.9 and 1.9 Hz), 9.70 (dd, 1H, indolizine-H, *J* 0.9 and 7.3 Hz).

^{13}C NMR ($CDCl_3$) 52.7 (CO_2CH_3), 113.1, 115.5, 120.8, 121.2, 124.3, 125.3, 126.0, 126.3, 126.7, 127.5, 127.9, 128.6, 133.1, 133.6, 134.6, 135.0, 135.5, 135.6, 141.9, 142.8, 162.1 (CO_2CH_3), 179.7 (quinone-*C*O), 180.5 (quinone-*C*O).

MS (FAB^+) 842 $(M+H)^+$, 841 $M^{+\bullet}$.

Anal. Calcd for $C_{56}H_{35}N_5O_4$: C, 79.89; H, 4.19; N, 8.32; Found: C, 79.89; H, 4.25; N, 8.32.

4.4.11: Synthesis of porphyrin-quinone 4.5 using K_2CO_3 as base

A toluene (6 mL) solution of pyridinium salt **4.4a** (20 mg), 1,4-naphthoquinone (82 mg, 20 equiv.) and K_2CO_3 (180 mg) was refluxed for 8 hours. TLC of the reaction mixture revealed the presence of two new products. The solvent was distilled under vacuum. The residue was separated by column chromatography (silica gel) using chloroform as eluent.

The first fraction isolated was the porphyrin-quinone **4.5** (0.8 mg, 4% yield). The second fraction isolated was the dealkylated compound **4.3a** (13.1 mg, 82% yield).

4.4.12: Dealkylation of pyridinium salt 4.4a by DBU

A toluene (6 mL) solution of pyridinium salt **4.4a** (20 mg) and DBU (0.19 mL) was refluxed for 8 hours. TLC of the reaction mixture revealed the dealkylated compound **4.3a** as the only product. After cooling the solution to room temperature, toluene was evaporated and the residue was separated by column chromatography (silica gel) using chloroform as eluent. Porphyrin **4.3a** (9.8 mg, 61% yield) was isolated.

4.4.13: Dealkylation of pyridinium salt 4.4a by K_2CO_3

A toluene (6 mL) solution of pyridinium salt **4.4a** (20 mg) and K_2CO_3 (180 mg) was refluxed for 8 hours. TLC of the reaction mixture revealed the dealkylated compound **4.3a** as the only product. After cooling the solution to room temperature, toluene was evaporated and the residue was separated by column chromatography (silica gel) using chloroform as eluent. Porphyrin **4.3a** (9.5 mg, 59% yield) was isolated.

4.4.14: Synthesis of porphyrin-quinone 4.6

A toluene (6 mL) solution of pyridinium salt **4.4a** (20 mg), 1,4-benzoquinone (56 mg, 20 equiv.) and K_2CO_3 (180 mg) was refluxed for 8 hours. TLC of the reaction mixture revealed two new products. After the solution was cooled to room temperature, toluene was evaporated and the residue was separated by column chromatography (silica gel) using

chloroform as eluent. The first fraction was porphyrin-quinone **4.6** (2.2 mg, 11% yield). The second fraction was dealkylation compound **4.3a** (5.2 mg, 32% yield).

mp > 300 ºC.

UV-Vis ($CHCl_3$) λ_{max} (log ε) 420 (5.43), 516 (4.23), 556 (3.95), 590 (3.78), 649 (3.61) nm.

^{1}H NMR ($CDCl_3$) −2.75 (s, 2H, N*H*), 4.18 (s, 3H, CO_2CH_3), 6.81 and 6.83 (AB, 2H, quinone C*H*, *J* 10.3 Hz), 7.74-7.80 (m, 9H, Ph-$H_{meta,para}$), 8.05 (dd, 1H, indolizine-H, *J* 1.9 and 7.3 Hz), 8.21-8.24 (m, 6H, Ph-H_{ortho}), 8.86 (AB, 4H, *β*-H, *J* 4.8 Hz), 8.90 (AB, 4H, *β*-H, *J* 4.8 Hz), 9.29 (dd, 1H, indolizine-H, *J* 0.9 and 1.9 Hz), 9.71 (dd, 1H, indolizine-H, *J* 0.9 and 7.3 Hz).

^{13}C NMR ($CDCl_3$) 52.6 (CO_2CH_3), 111.7, 114.2, 115.3, 120.8, 121.2, 124.0, 125.1, 125.3, 126.8, 126.9, 127.9, 131.4, 131.8, 134.5, 134.6, 135.0, 139.2, 141.89, 141.91, 143.1, 146.4, 161.8 (CO_2CH_3), 181.3 (quinone-*C*O), 182.1 (quinone-*C*O).

MS (FAB$^+$) 794 $(M+3H)^+$, 793 $(M+2H)^{+\bullet}$.

Anal. Calcd. for $C_{52}H_{33}N_5O_4$: C, 78.87; H, 4.20; N, 8.84; Found: C, 78.91; H, 4.23; N, 8.75.

4.4.15: Synthesis of porphyrin-quinone 4.7

A toluene (6 mL) solution of pyridinium salt **4.4a** (20 mg), 1,4-benzoquinone (56 mg, 20 equiv.) and DBU (0.19 mL) was refluxed for 8 hours. TLC of the reaction mixture revealed the presence of two new products. After the solution was cooled to room temperature, toluene was evaporated and the residue was separated by column chromatography (silica gel) using chloroform as eluent. The first fraction was porphyrin-quinone **4.7** (3.1 mg, 16% yield). The second fraction was dealkylation compound **4.3a** (3.0 mg, 19% yield).

mp > 300 ºC.

UV-Vis ($CHCl_3$) λ_{max} (log ε) 419 (5.80), 517 (4.67), 557 (4.45), 590 (4.18), 649 (4.06) nm.

^{1}H NMR ($CDCl_3$) −2.86 (s, 4H, N*H*), 4.27 (s, 6H, CO_2CH_3), 7.64-7.73 (m, 18H, Ph-$H_{meta,para}$), 7.99 (dd, 2H, indolizine-H, *J* 1.9 and 7.3 Hz), 8.07-8.15 (m, 12H, Ph-H_{ortho}),

8.77 (AB, 8H, *β*-H, *J* 5.2 Hz), 8.81 (d, 4H, *β*-H, *J* 4.9 Hz), 8.93 (d, 4H, *β*-H, *J* 4.9 Hz), 9.38 (dd, 2H, indolizine-H, *J* 0.8 and 1.9 Hz), 9.61 (dd, 2H, indolizine-H, *J* 0.8 and 7.3 Hz). ^{13}C NMR ($CDCl_3$) δ 52.7 (CO_2CH_3), 114.6, 114.7, 115.8, 117.7, 120.5, 120.9, 122.4, 123.8, 125.0, 125.9, 126.6, 127.4, 127.7, 130.2, 131.1, 131.2, 131.3, 131.4, 131.6, 134.5, 134.7, 137.5, 141.7, 141.87, 141.90, 162.2 (CO_2CH_3), 177.5 (quinone-*C*O), 177.9 (quinone-*C*O). MS (FAB$^+$) 1475 $(M+H)^+$, 1474 $M^{+\bullet}$.
Anal. Calcd for $C_{98}H_{62}N_{10}O_6$: C, 79.77; H, 4.24; N, 9.49; Found: C, 79.86; H, 4.15; N, 9.32.

4.4.16: Cycloaddition reaction of the *meta*-isomer 4.4b with 1,4-naphthoquinone

A toluene (6 mL) solution of pyridinium salt **4.4b** (20 mg), 1,4-naphthoquinone (82 mg, 20 equiv.) and DBU (0.19 mL) was refluxed for 8 hours. TLC of the reaction mixture revealed the presence of three new products. After the solution was cooled to room temperature, toluene was evaporated and the residue was separated by column chromatography (silica gel) using chloroform as eluent. The first fraction was a mixture of porphyrin-quinone isomers **4.9** (2.1 mg, 10% yield) and **4.10** (1.0 mg, 5% yield) which was separated by preparative TLC. The second fraction was dealkylation compound **4.3b** (4.5 mg, 28% yield).

4.9:
mp > 300 ºC.
UV-Vis ($CHCl_3$) λ_{max} (% rel. intensity) 420 (100%), 515 (7%), 551 (4%), 590 (3%), 645 (2%) nm.
^{1}H NMR ($CDCl_3$) -2.77 (s, 2H, N*H*), 4.01 (s, 3H, CO_2CH_3), 7.73-7.82 (m, 11H, naphthoquinone-H and Ph-$H_{meta,para}$), 8.21-8.24 (m, 6H, Ph-H_{ortho}), 8.32-8.39 (m, 2H, naphthoquinone-H), 8.41 (dd, 1H, indolizine-H, *J* 1.5 and 9.1 Hz), 8.87-8.94 (m, 8H, *β*-H), 9.01 (dd, 1H, indolizine-H, *J* 0.9 and 9.1 Hz), 10.13 (br s, 1H, indolizine-H).
^{13}C NMR ($CDCl_3$) 52.6 (CO_2CH_3), 112.9, 113.1, 114.8, 118.3, 120.7, 121.2, 126.3, 126.7, 126.8, 127.5, 127.9, 128.3, 131.1, 131.5, 132.5, 133.2, 133.7, 134.6, 134.7, 135.0, 135.5, 135.7, 141.8, 141.9, 161.8 (CO_2CH_3), 179.9 (quinone-*C*O), 180.4 (quinone-*C*O).

MS (FAB$^+$) 842 $(M+H)^+$, 841 $M^{+\bullet}$.

HRMS (FAB$^+$) Calcd for $C_{56}H_{36}N_5O_4$ $(M+H)^+$ 842.2767; Found 842.2757.

4.10:

mp > 300 ºC.

UV-Vis ($CHCl_3$) λ_{max} (% rel. intensity) 421 (100%), 517 (8%), 553 (5%), 593 (4%), 649 (3%) nm.

^{1}H NMR ($CDCl_3$) -2.52 (s, 2H, N*H*), 4.25 (s, 3H, CO_2CH_3), 6.58 (dd, 1H, naphthoquinone-H, *J* 1.1 and 7.5 Hz), 7.01 (dt, 1H, naphthoquinone-H, *J* 1.1 and 7.5 Hz), 7.35 (t, 1H, naphthoquinone-H, *J* 7.5 Hz), 7.48 (t, 1H, indolizine-H, *J* 7.1 Hz), 7.70-7.78 (m, 9H, Ph-$H_{meta,para}$), 7.99-8.03 (m, 2H, indolizine-H and naphthoquinone-H), 8.15-8.25 (m, 6H, Ph-H_{ortho}), 8.64 (d, 2H, β-H, *J* 4.8 Hz), 8.76 (d, 2H, β-H, *J* 4.8 Hz), 8.84 (AB, 4H, *J* 5.2 Hz), 9.56 (dd, 1H, indolizine-H, *J* 0.6 and 7.1 Hz).

MS (FAB$^+$) 842 $(M+H)^+$, 841 $M^{+\bullet}$.

HRMS (FAB$^+$) Calcd for $C_{56}H_{36}N_5O_4$ $(M+H)^+$ 842.2767; Found 842.2780.

4.4.17: Cycloaddition reaction of porphyrin 4.4a with dimethyl acetylenedicarboxylate using K_2CO_3 as base

A toluene (6 mL) solution of pyridinium salt **4.4a** (20 mg), dimethyl acetylenedicarboxylate (74 mg, 20 equiv.) and K_2CO_3 (180 mg) was refluxed for 8 hours. TLC of the reaction mixture revealed the presence of two main products and various compounds with small amounts. After the solution was cooled to room temperature, toluene was evaporated and the residue was separated by column chromatography (silica gel) using chloroform as eluent. The first fraction isolated was porphyrin **4.12** (3.2 mg, 17% yield). The second fraction isolated was porphyrin **4.11** (4.3 mg, 20% yield). The dealkylated compound **4.3a** (0.4 mg, 2% yield) was also isolated in small amount.

4.11:

mp 273-274 ºC.

UV-Vis ($CHCl_3$) λ_{max} (log ε) 417 (5.32), 516 (4.30), 553 (3.99), 590 (3.78), 646 (3.63) nm.

^{1}H NMR ($CDCl_3$) -2.76 (s, 2H, N*H*), 3.80, 4.05 and 4.11 (3s, 9H, 3 × CO_2CH_3), 7.73-7.79 (m, 9H, Ph-$H_{meta,para}$), 8.00 (dd, 1H, indolizine-H, *J* 1.9 and 7.2 Hz), 8.21-8.24 (m, 6H, Ph-H_{ortho}), 8.86-8.92 (m, 8H, *β*-H), 9.14 (dd, 1H, indolizine-H, *J* 0.9 and 1.9 Hz), 9.87 (dd, 1H, indolizine-H, *J* 0.9 and 7.2 Hz).

^{13}C NMR ($CDCl_3$) 51.7 (CO_2CH_3), 52.2 (CO_2CH_3), 53.1 (CO_2CH_3), 103.8, 112.1, 116.0, 120.7, 121.1, 122.4, 124.8, 125.2, 126.71, 126.74, 127.8, 131.6, 134.5, 136.7, 141.3, 141.88, 141.93, 160.7 (CO_2CH_3), 163.4 (CO_2CH_3), 166.3 (CO_2CH_3).

MS (FAB$^+$) 828 $(M+H)^+$, 827 $M^{+\bullet}$.

HRMS (ESI) Calcd for $C_{52}H_{38}N_5O_6$ $(M+H)^+$ 828.2817; Found 828.2786.

4.12:

mp 228-229 ºC.

UV-Vis ($CHCl_3$) λ_{max} (log ε) 415 (5.41), 515 (4.31), 550 (3.92), 589 (3.77), 645 (3.57) nm.

^{1}H NMR ($CDCl_3$) -2.81 (s, 2H, N*H*), 3.98 and 4.11 (2s, 6H, 2 × CO_2CH_3), 7.73-7.80 (m, 9H, Ph-$H_{meta,para}$), 8.14 (d, 1H, H-5, *J* 7.9 Hz), 8.20-8.23 (m, 6H, Ph-H_{ortho}), 8.40 (dd, 1H, H-6, *J* 1.7 and 7.9 Hz), 8.59 (d, 1H, H-2, *J* 1.7 Hz), 8.77 (d, 2H, *β*-H, *J* 4.8 Hz), 8.86-8.89 (m, 6H, *β*-H).

^{13}C NMR ($CDCl_3$) 52.9 (CO_2CH_3), 53.0 (CO_2CH_3), 117.0, 120.5, 120.8, 126.7, 127.4, 127.8, 130.5, 131.2, 134.3, 134.5, 136.7, 141.9, 142.0, 145.5, 168.1 (CO_2CH_3), 168.3 (CO_2CH_3).

MS (FAB$^+$) 731 $(M+H)^+$, 730 $M^{+\bullet}$.

4.4.18: Cycloaddition reaction of porphyrin 4.4a with dimethyl acetylenedicarboxylate using DBU as base

A toluene (6 mL) solution of pyridinium salt **4.4a** (20 mg), dimethyl acetylenedicarboxylate (74 mg, 20 equiv.) and DBU (0.19 mL) was refluxed for 8 hours.

TLC of the reaction mixture revealed the presence of a main product and various compounds in small amounts. After cooling the solution to room temperature, toluene was evaporated and the residue was separated by column chromatography (silica gel) using chloroform as eluent. The first fraction isolated was porphyrin **4.11** (8.4 mg, 39% yield). The dealkylated compound **4.3a** (0.3 mg, 2% yield) was isolated from the second fraction.

4.4.19: Synthesis of π-extended porphyrin 4.17

A toluene (6 mL) solution of pyridinium salt **4.4a** (20 mg), *N*-methyl maleimide (58 mg, 20 equiv.) and DBU (0.19 mL) was refluxed for 8 hours. TLC of the reaction mixture revealed the presence of two products. After cooling the solution to room temperature, toluene was evaporated and the residue was separated by column chromatography (silica gel) using chloroform as eluent. The first fraction isolated was the dealkylated compound **4.3a** (2.3 mg, 14% yield). The second fraction isolated was a green compound, the π-extended porphyrin **4.17** (4.9 mg, 31% yield).

UV-Vis ($CHCl_3$) λ_{max} (log ε) 446 (5.03), 470 (5.08), 495 (4.44), 637 (3.87), 741 (3.47) nm.
^{1}H NMR ($CDCl_3$) –0.34 (s, 1H, N*H*), 1.22 (s, 1H, N*H*), 7.63 (br d, 1H, Py-H, *J* 4.8 Hz), 7.67-7.74 (m, 10H, Ph-H$_{meta,para}$ and *β*-H), 8.00-8.03 (m, 6H, Ph-H$_{ortho}$), 8.16 (d, 1H, Py-H, *J* 4.8 Hz), 8.24 (d, 1H, *β*-H, *J* 4.7 Hz), 8.28 (br s, 1H, Py-H), 8.29 (d, 1H, *β*-H, *J* 4.7 Hz), 8.33 (dd, 1H, *β*-H, *J* 1.9 and 4.7 Hz), 8.38 (dd, 1H, *β*-H, *J* 1.8 and 4.7 Hz), 8.58 (dd, 1H, *β*-H, *J* 1.4 and 5.0 Hz), 8.86 (dd, 1H, *β*-H, *J* 1.2 and 5.0 Hz).
^{13}C NMR ($CDCl_3$) 107.5, 118.6, 121.4, 122.1, 124.3, 124.7, 126.15, 126.18, 126.8, 127.1, 127.2, 127.9, 128.0, 128.3, 131.4, 133.2, 133.3, 133.6, 134.0, 134.2, 135.5, 139.2, 140.8, 141.7, 143.8, 147.3, 151.6, 158.6.
MS (FAB$^+$) 614 $(M+H)^+$, 613 $M^{+\bullet}$.

4.4.20: Synthesis of porphyrin 4.18

A toluene (6 mL) solution of pyridinium salt **4.4a** (20 mg), *N*-methyl maleimide (58 mg, 20 equiv.) and K_2CO_3 (180 m) was refluxed for 8 hours. TLC of the reaction mixture revealed the presence of a main product and various compounds with small amounts. After cooling the solution to room temperature, toluene was evaporated and the residue was separated by column chromatography (silica gel) using chloroform as eluent. The porphyrin **4.18** (3.3 mg, 14% yield) was isolated.

UV-Vis ($CHCl_3$) λ_{max} (log ε) 430 (5.57), 533 (4.02), 572 (4.36), 600 (3.93), 654 (3.42) nm.
^{1}H NMR ($CDCl_3$) –2.52 (s, 1H, N*H*), –1.55 (s, 1H, N*H*), 2.38 (s, 3H, NCH_3), 3.13-3.18 (m, 4H, H-2^{7c} and NCH_3), 3.80 (dd, 1H, H-2^{6a}, *J* 8.3 and 9.8 Hz), 3.91 (s, 3H, CO_2CH_3), 3.95 (t, 1H, H-2^{7d}, *J* 7.6 Hz), 4.50 (d, 1H, H-2^{3c}, *J* 8.3 Hz), 4.78 (dd, 1H, H-2^{6b}, *J* 2.0 and 9.8 Hz), 4.95 (d, 1H, H-2^{3a}, *J* 7.6 Hz), 5.07 (ddd, 1H, H-2^{7b}, *J* 1.7, 3.2 and 10.0 Hz), 7.62 (dd, 1H, H-2^7, *J* 2.0 and 3.2 Hz), 7.71-7.81 (m, 9H, Ph-H$_{meta,para}$), 8.11-8.30 (m, 6H, Ph-H$_{ortho}$), 8.68 (d, 1H, *β*-H, *J* 4.7 Hz), 8.73 (d, 1H, *β*-H, *J* 4.7 Hz), 8.81 (d, 1H, *β*-H, *J* 1.7 Hz), 8.83 (dd, 1H, *β*-H, *J* 1.8 and 4.9 Hz), 8.90 (dd, 1H, *β*-H, *J* 1.5 and 4.9 Hz), 9.05 (d, 1H, *β*-H, *J* 4.8 Hz), 9.63 (d, 1H, *β*-H, *J* 4.8 Hz).
^{13}C NMR ($CDCl_3$) 25.3 (N*C*H$_3$), 25.5 (N*C*H$_3$), 44.5 (C-2^{7b}), 47.3 (C-2^{3a}), 47.5 (C-2^{7d}), 51.0 (C-2^{3c}), 51.5 (C-2^{6a}), 54.0 (CO_2*C*H$_3$), 62.0 (C-2^{6b}), 64.5 (C-2^{7c}), 80.7 (C-2^{3b}), 113.6, 120.7 (C-2^7), 121.2, 121.4, 122.6, 126.5, 126.8, 127.2, 127.4, 127.7, 127.8, 129.0, 129.8, 134.1, 134.3, 134.4, 134.5, 134.6, 134.8, 140.5, 141.7, 142.6, 148.6, 150.1, 170.4 (*C*O), 175.1 (*C*O), 175.4 (*C*O), 176.1 (*C*O), 177.3 (*C*O).
MS (FAB$^+$) 908 (M+H)$^+$, 907 M $^{+\bullet}$.

4.4.21: Cycloaddition reaction of porphyrin 4.4a with dimethyl fumarate

A toluene (6 mL) solution of pyridinium salt **4.4a** (20 mg), dimethyl fumarate (75 mg, 20 equiv.) and DBU (0.19 mL) was refluxed for 8 hours. TLC of the reaction mixture revealed the presence of two main products and various compounds in trace amounts. After cooling the solution to room temperature, toluene was evaporated and the residue was separated by column chromatography (silica gel) using chloroform as eluent. The first fraction isolated was a green compound, the π-extended porphyrin **4.19** (0.8 mg, 4% yield). The second fraction was **4.17** (0.9 mg, 6% yield).

UV-Vis ($CHCl_3$) λ_{max} (% rel. intensity) 376 (24%), 422 (34%), 476 (100%), 512 (30%), 587 (12%), 636 (17%), 711 (15%) nm.
^{1}H NMR ($CDCl_3$) –1.01 (s, 1H, N*H*), 0.27 (s, 1H, N*H*), 3.96, 4.04 and 4.11 (3s, 9H, 3 × CO_2CH_3), 7.67-7.78 (m, 9H, Ph-H$_{meta,para}$), 8.02-8.16 (m, 6H, Ph-H$_{ortho}$), 8.18 (s, 1H, H-2^5), 8.43 (AB, 2H, *β*-H, *J* 4.8 Hz), 8.54 (dd, 1H, *β*-H, *J* 1.8 and 4.8 Hz), 8.63 (dd, 1H, *β*-H, *J* 1.4 and 4.8 Hz), 8.83 (d, 1H, *β*-H, *J* 5.0 Hz), 9.13 (s, 1H, H-2^8), 9.42 (d, 1H, *β*-H, *J* 5.0 Hz), 9.48 (s, 1H, *β*-H).
MS (FAB$^+$) 826 $(M+H)^+$, 825 $M^{+\bullet}$.

4.4.22: Cycloaddition reaction of porphyrin 4.4a with dimethyl maleate

A toluene (6 mL) solution of pyridinium salt **4.4a** (20 mg), dimethyl maleate (75 mg, 20 equiv.) and DBU (0.19 mL) was refluxed for 8 hours. TLC of the reaction mixture revealed the presence of two main products and various compounds in trace amounts. After cooling the solution to room temperature, toluene was evaporated and the residue was separated by column chromatography (silica gel) using chloroform as eluent. The first fraction was a green compound, the π-extended porphyrin **4.19** (0.5 mg, 2% yield). The second fraction was **4.17** (5.4 mg, 34% yield).

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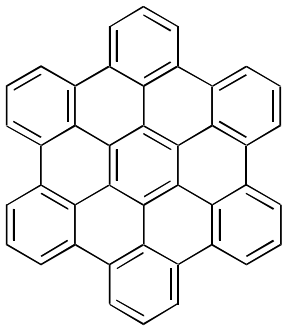
Chapter 5: Synthesis of polycyclic aromatic porphyrin analogues *via* electrocyclic reactions

5.1: Polycyclic aromatic hydrocarbon and its porphyrin analogues

Polycyclic aromatic hydrocarbons (PAHs) have attracted the attention of synthetic, theoretical and industrial chemists,[1] since these compounds can be interesting building blocks for the preparation of materials that can be used as molecular devices, liquid crystals, and other electronic and optoelectronic devices.[2]

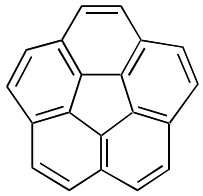
Among the polycyclic aromatic hydrocarbons, the all-benzenoid analogues constitute only a small group. A well-known example is hexa-*peri*-hexabenzocoronene (HBC). Due to its hexagonal symmetry, it is described as the "superbenzene", where each peripheral benzene ring is equal to one sp^2-carbon of benzene.[3] HBC serves as an intriguing homologue of benzene with unique electronic properties. Larger PAHs than HBC are also accessible and constitute certain molecularly defined models of graphites.[4]



HBC

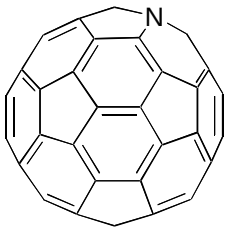
Isolation of C_{60} (buckminsterfullerene) as well as higher fullerenes have brought renewed interest in the chemistry of bow-shaped polycyclic aromatic hydrocarbons,[5] which have also been named as 'fullerene fragments', 'buckybowls' or 'open geodesic polyarenes'.[6] The simplest member of this family is corannulene, a $C_{20}H_{10}$ hydrocarbon

representing the polar cap of C_{60}.[7] The bowl-shaped PAHs have potential use as starting materials for the development of synthesis of the fullerenes, as an alternative to those based on the vaporization of graphite.[8]



Corannulene

Since the discovery of the fullerenes, synthetic chemists have been fascinated by the idea of developing chemical modification of the all-carbon cages.[9] Apart from exohedral and endohedral fullerene derivatives, heterofullerenes represent the third fundamental group of modified fullerenes.[10] The simplest representative of heterofullerenes is hydroaza[60]fullerene $C_{59}NH$, which was synthesized from C_{60}.[11] Therefore, the heterocyclic analogues of PAHs can be treated as the fragments of heterofullerenes.



Hydroaza[60]fullerene

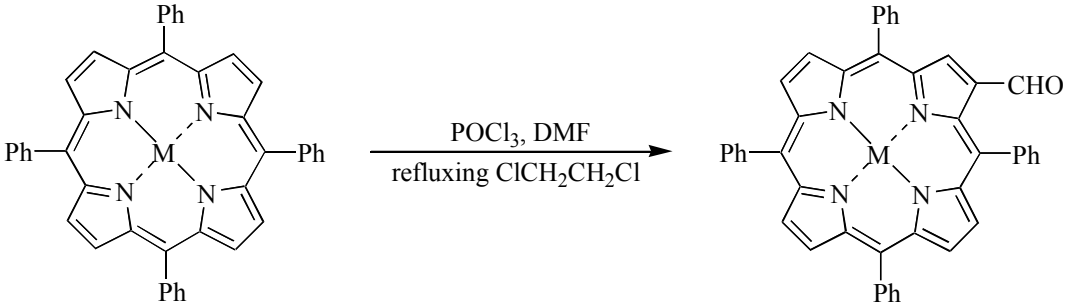
Recently, our group and others have exploited a new class of porphyrin analogues – *meso*+β fused porphyrins (see Chapters 3 and 4).[12] Those compound have potential biomedical and material applications due to the absorption in the near-infrared region. On the other hand, these polycyclic porphyrin analogues also can be treated as heterocyclic analogues of PAHs. Therefore, these compounds have potential use as subunits of two dimension and three dimension porphyrin derivatives similar to graphites, fullerenes, and nanotubes. This development could bring a new stimulus for porphyrin chemistry.

5.2: Synthesis of polycyclic aromatic porphyrin analogues

Callot *et al.* have extensively investigated the *meso*+β fused porphyrins.[13] However, in these examples the fused rings are not usually aromatic rings. We therefore synthesized polycyclic aromatic porphyrin analogues from the ketone-bridged porphyrins (see Chapter 2).

5.2.1: Synthesis of starting porphyrins

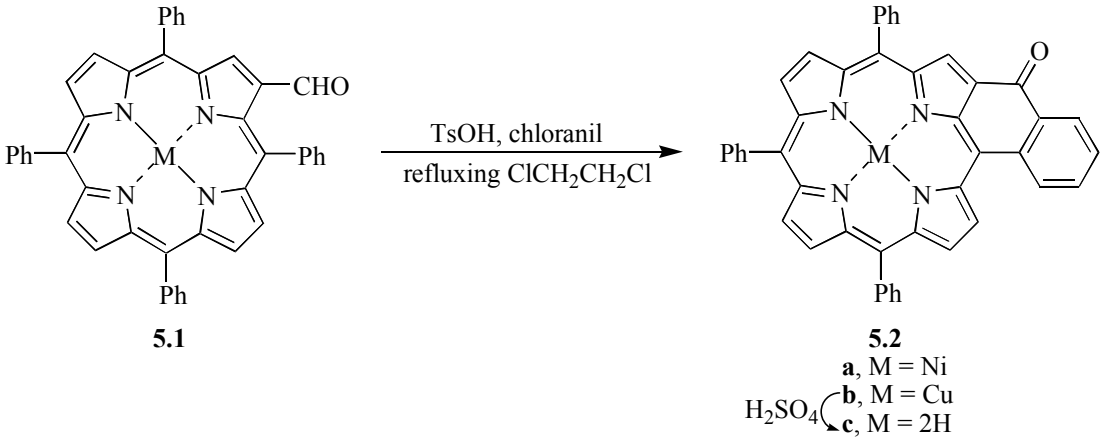
Peripheral functionalization of porphyrins has been achieved in many cases *via* a formyl group. Vilsmeier formylation, in which phosphorus oxychloride and *N*,*N*-dimethylformamide are used to form an iminium complex which is subsequently hydrolyzed, is the most convenient method for the introduction of this functional group. Usually, it is carried out on Cu(II) or Ni(II) complexes.[14] NiTPP reacted with Vilsmeier reagent in refluxing dichloroethane to give, after basic hydrolysis of the iminium salt, Ni(2-formylTPP) **5.1a** in 78% yield (Scheme 5.1). The structure was confirmed by its UV-Vis and ^{1}H NMR spectra. Its UV-Vis spectrum shows bands at λ_{max} 430, 541 and 583 nm. In its ^{1}H NMR spectrum, the protons of the *meso*-phenyl groups appear as two multiplets at δ 7.66-7.75 (12H, *meta* and *para*-H) and δ 7.94-8.04 ppm (8H, *ortho*-H). The seven β-pyrrolic protons appear as one multiplet at δ 8.66-8.77 (6H) and a singlet at δ 9.16 ppm (1H). The formyl group proton appears as a singlet at δ 9.31 ppm.



5.1
a, M = Ni
b, M = Cu

Scheme 5.1

However, demetalation of **5.1** in strong acid has been shown to result in intramolecular cyclizations involving the carbonyl group and the *ortho* position of the adjacent phenyl group (see Chapter 2).[15] The ketone-bridged porphyrins **5.2** were usually obtained under oxidative conditions as described by Ishkov and Zhilina,[15b] to optimize the conversion to the ketone (Scheme 5.2). The porphyrin **5.2a** was isolated in 40% yield. Porphyrin **5.2c** was obtained from the demetalation of porphyrin **5.2b** by using sulfuric acid. The ^{1}H NMR, UV-Vis and mass spectra are fully consistent with the proposed structure. Its UV-Vis spectrum shows bands at λ_{max} 380, 463 and 646 nm. The addition of two unsaturated rings in the plane of the porphyrin and the corresponding extension of the conjugation induce the interesting red shift. The mass spectrum shows intense peaks at *m/z* 697 ($[M+H]^+$) and 696 ($[M]^{+\bullet}$), 2 Da less than **5.1a**, confirming that it is an oxidative coupling compound. A proton of the fused phenyl group appear as a double triplet at δ 7.37 ppm (*J* 0.9 and 7.5 Hz). The protons of three *meso*-phenyl groups and two protons of the fused phenyl group appear as two multiplets at δ 7.56-7.70 (10H, *meta* and *para*-H and fused Ph-H) and δ 7.78-7.88 ppm (7H, *ortho*-H and fused Ph-H). The other fused phenyl proton and two β-pyrrolic protons appear as one multiplet at δ 8.31-8.36 ppm (3H). The remaining five β-pyrrolic protons appear as four doublets at δ 8.43 (*J* 5.0 Hz), 8.45 (*J* 5.0 Hz), 8.53 (*J* 5.1 Hz) and 9.08 ppm (*J* 5.1 Hz) and a singlet at δ 9.06 ppm.



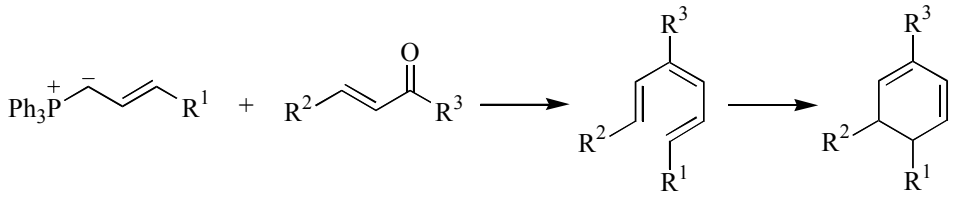
5.1

5.2
a, M = Ni
b, M = Cu
c, M = 2H

Scheme 5.2

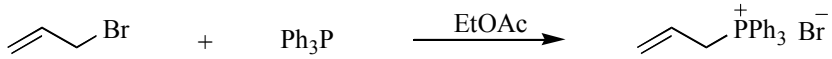
It has been shown that the reactions of allylic phosphorus ylides with α,β-unsaturated ketones (aldehydes) afforded 1,3-cycloalkadienes (Scheme 5.3).[16] The initial Wittig

reaction was followed by the electrocyclic cyclization to give the product. Porphyrins **5.2** can be treated as α,β-unsaturated ketones. Therefore, we could obtain the polycyclic aromatic porphyrin analogues from the aromatization of the resulting 1,3-cycloalkadienes.



Scheme 5.3

To initiate this study, we synthesized the phosphonium salt **5.3** using a similar procedure to the one related with the synthesis of pyridinium salts (Scheme 5.4). It was obtained as a white solid in 89% yield. The structure was confirmed by ^{1}H NMR. The methylene protons appear as a double doublet at δ 4.83 ppm (*J* 6.7 and 15.6 Hz), The three alkenyl protons appear as two multiplets at δ 5.38-5.43 (1H) and 5.56-5.77 ppm (2H). The phenyl protons appear as a multiplet at δ 7.69-7.89 ppm.



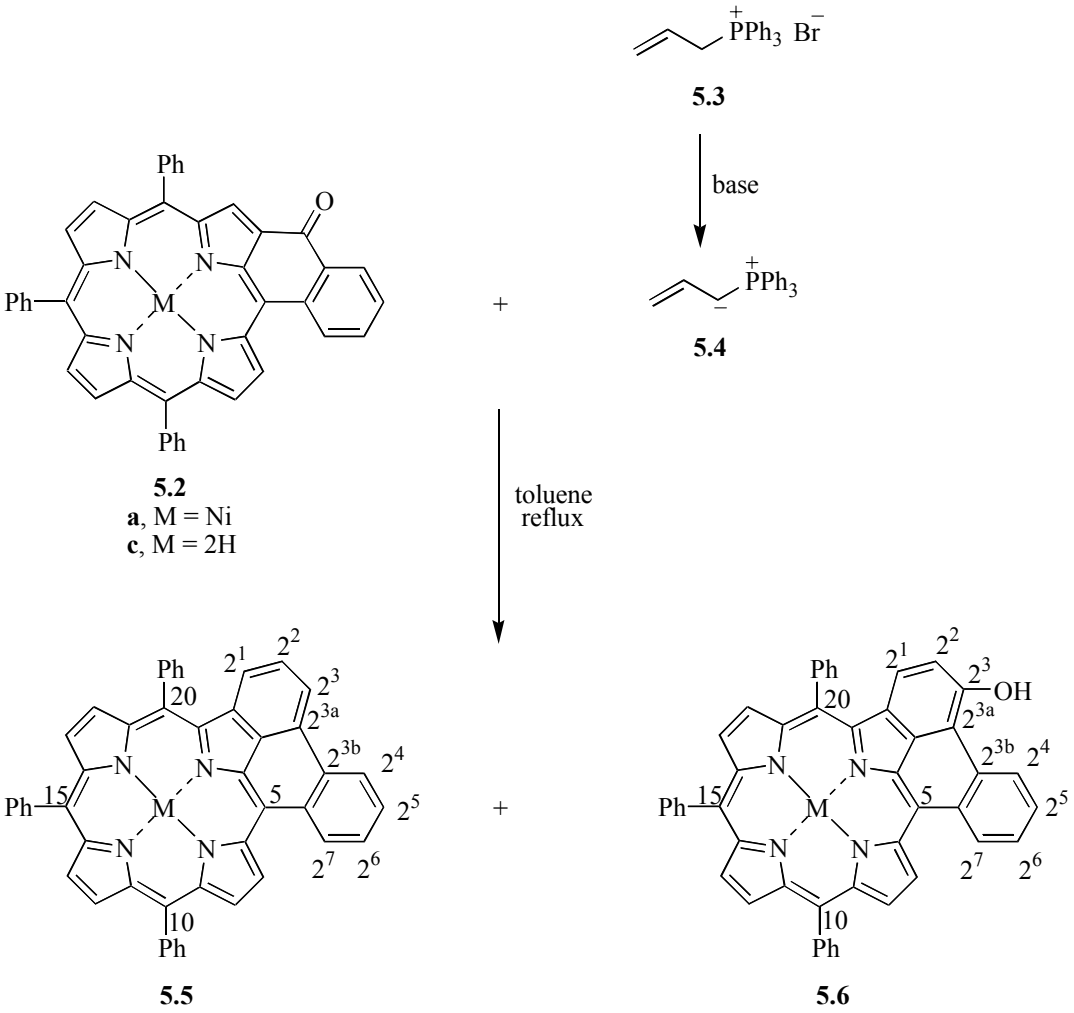
5.3

Scheme 5.4

5.2.2: Synthesis of polycyclic aromatic porphyrin analogues

Reactions of porphyrins **5.2** with two equivalents of allylic phosphorus ylide **5.4** were carried out in refluxing toluene (Scheme 5.5). The phosphorus ylide **5.4** was generated *in situ* from phosphonium salt **5.3** with a base. However, when potassium carbonate was used as base, for the reaction of ketone **5.2a**, together with the expected porphyrin **5.5a** (11% yield), porphyrin **5.6a** was generated in 27% yield after two days of reaction time (for the reaction of ketone **5.2c**, the expected porphyrin **5.5c** was obtained in 26% yield and porphyrin **5.6c** was isolated in 19% yield). When sodium hydride was used as base,

porphyrin **5.5a** was obtained in 16% yield and porphyrin **5.6a** was isolated in 3% yield after 12 hours of reaction time (porphyrin **5.5c** was obtained in 12% yield and porphyrin **5.6c** was isolated in 3% yield after 12 hours).



Scheme 5.5

The UV-Vis, mass spectra and full NMR study (^{1}H, ^{13}C, COSY, NOESY, HSQC, and HMBC) allowed us to establish the structures of the new products.

The UV-Vis spectrum of **5.5a** shows a pronounced red shift of both Soret and Q bands (λ_{max} 445, 562 and 612 nm) relative to the corresponding one of NiTPP. The FAB mass spectrum shows intense peaks at *m/z* 719 ($[M+H]^+$) and 718 ($[M]^{+\bullet}$). In the ^{1}H NMR spectrum (Fig. 5.1), the six β-pyrrolic protons appear as one AB spin system at δ 8.67 ppm (2H, *J* 4.9 Hz) and four doublets at δ 8.53 (*J* 4.8 Hz), 8.60 (*J* 4.8 Hz), 8.89 (*J* 4.9 Hz) and

9.51 ppm (H-7, *J* 4.9 Hz). The protons H-2^4 and H-2^7 appear as a doublet at δ 8.98 ppm (2H, *J* 8.1 Hz), which couple with the H-2^6 (or H-2^5) at δ 7.93-7.98 (multiplet, 1H) and the other proton under the multiplet at δ 7.78-7.85 ppm (4H, H-2^5 or H-2^6, and Ph-$H_{meta,para}$). From the NOESY spectrum, the NOE effect between the β-proton H-7 and the proton H-2^7 is observed. The proton H-2^1 appears as a doublet at δ 7.35 (1H, *J* 7.7 Hz). The proton H-2^3 appears as a doublet at δ 8.88 ppm (1H, *J* 7.7 Hz), which is confirmed by a NOE cross peak between the proton H-2^3 and H-2^4 under the doublet at δ 8.98 ppm. The protons H-2^1 and H-2^3 couple with H-2^2 under the multiplet at δ 7.98-8.03 ppm (7H, H-2^2 and Ph-H_{ortho}). The observed multiplet at δ 7.66-7.70 ppm (6H) corresponds to *meta*-H and *para*-H of the *meso*-phenyl groups.

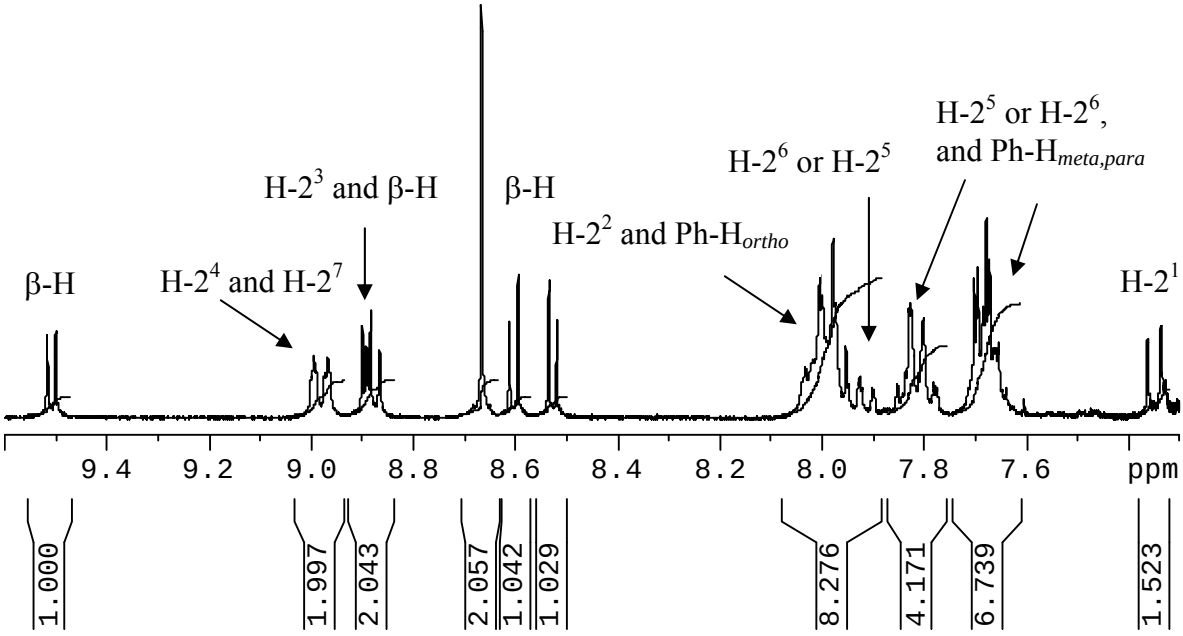


Figure 5.1 ^{1}H NMR spectrum of porphyrin 5.5a

Similarly, the UV-Vis spectrum of **5.6a** shows bands at λ_{max} 444, 558 and 617 nm. The FAB mass spectrum shows intense peaks at *m/z* 735 ($[M+H]^+$) and 734 ($[M]^{+\bullet}$), indicating one more oxygen atom for **5.6a** than for **5.5a**. In the ^{1}H NMR spectrum (Fig. 5.2), the six β-pyrrolic protons appear as six doublets at δ 8.52 (*J* 4.8 Hz), 8.58 (*J* 4.8 Hz), 8.59 (*J* 4.8

Hz), 8.64 (*J* 4.8 Hz), 8.83 (*J* 4.9 Hz) and 9.39 ppm (H-7, *J* 4.9 Hz). The proton H-2^7 appears as one doublet at δ 8.86 ppm (*J* 7.8 Hz), which is confirmed by a NOE cross peak between the proton H-2^7 and the β-pyrrolic proton at H-7. The proton H-2^4 appears as one doublet at δ 9.55 ppm (*J* 7.8 Hz). The protons H-2^5, H-2^6 and the protons of three *meso*-phenyl groups appear as two multiplets at δ 7.61-7.89 (11H, H-2^5, H-2^6, *meta* and *para*-H), and 7.91-7.99 ppm (6H, *ortho*-H). The proton H-2^1 appears as one doublet at δ 7.04 ppm (*J* 8.2 Hz), which is confirmed by a NOE cross peak between the proton H-2^1 and the *ortho*-H of the adjacent *meso*-phenyl group under the multiplet at δ 7.91-7.99 ppm. The proton H-2^2 appears as one doublet at δ 7.11 ppm (*J* 8.2 Hz). The OH proton appears as a broad singlet at δ 6.23 ppm, and this signal disappears after shaking with deuterium oxide.

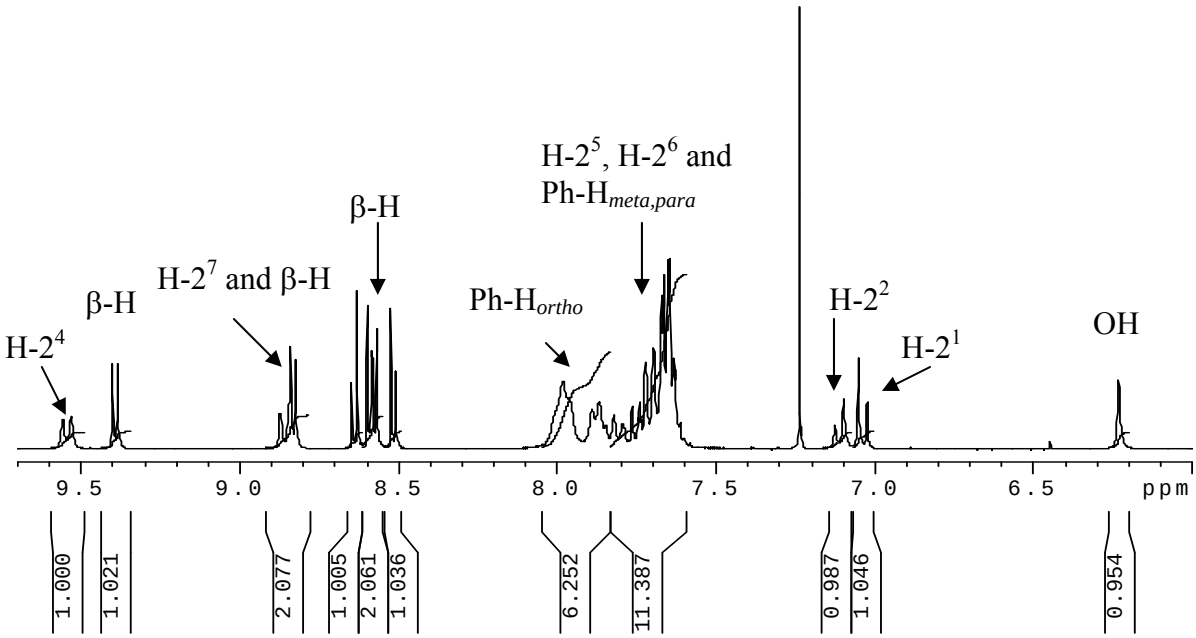


Figure 5.2 ^{1}H NMR spectrum of porphyrin 5.6a

The fusion of two phenyl rings has a large effect on the UV-Vis spectra of porphyrins **5.5c** and **5.6c** (Fig. 5.3). Firstly, the addition of aromatic rings fused to the core of the porphyrin leads to an extension of the conjugated system, thus leading to a bathochromic shift. Secondly, fusing additional rings leads to large deformation of the porphyrin core. In

general, these distortions are known to induce bathochromic shifts in the UV-Vis spectra of porphyrins, however, these shifts occur concomitantly with a general lowering of the extinction coefficients.[17] Compared to those *meso*+β fused porphyrins described in Chapter 3 and Chapter 4, which have strong absorptions in the visible region above 700 nm, the absorptions of porphyrins **5.5c** and **5.6c** do not reach 700 nm since the fused rings are phenyl rings instead of heterocycles.

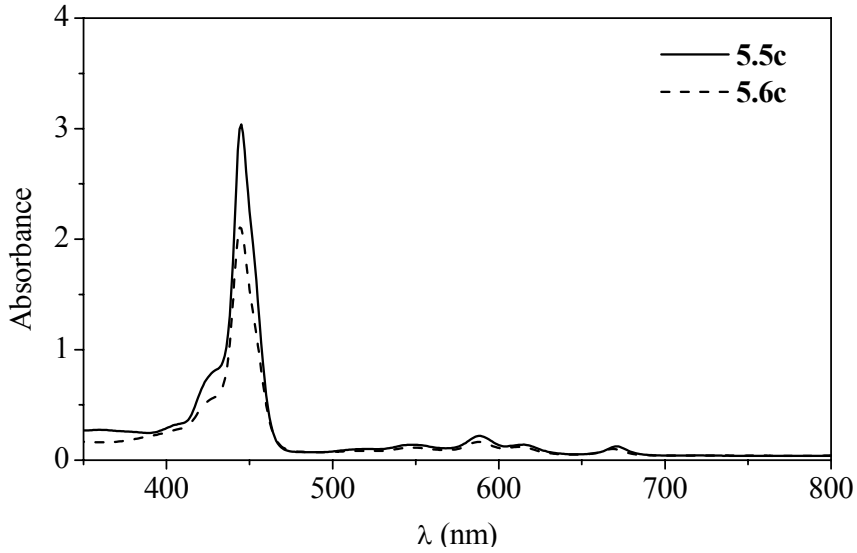
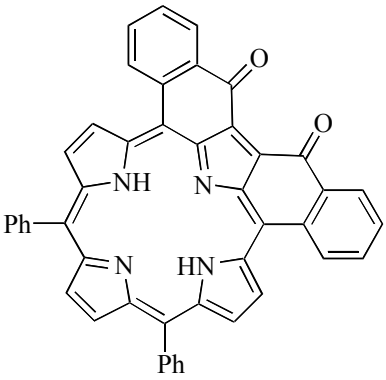
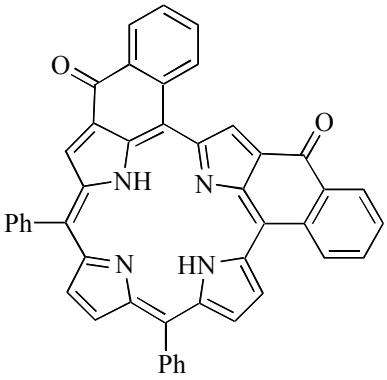


Figure 5.3 UV-Vis spectra of porphyrins 5.5c and 5.6c

The formylation of *meso*-tetraphenylporphyrins produces several oligoaldehydes,[18] which can be used to prepare some diketones similar to **5.2**. Callot *et al.* synthesized six possible diketones **5.7**-**5.12** by the Friedel-Crafts acylation of porphyrins.[19] These porphyrins represent potential starting materials for the polycyclic aromatic porphyrin analogues, which have two phenyl rings fused at adjacent or opposite pyrrolic rings. The absorptions in the UV-Vis spectra could reach the NIR region. These polycyclic aromatic porphyrin analogues have different bridging features with the porphyrin analogues described by Smith and Zaleski groups.[12b-d] Zaleski *et al.* have reported that attempted synthesis of full fused porphyrin analogues such as **5.13** from the Bergman cyclization of octakis(phenylethynyl)porphyrins has failed.[20] But such procedure has potentialities for the synthesis of full fused porphyrin analogues.



5.7



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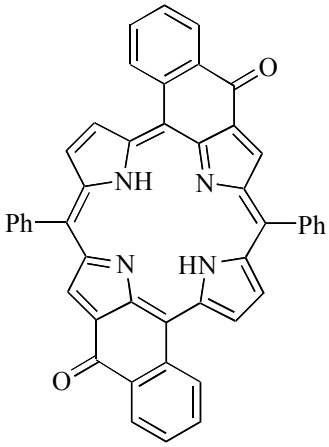

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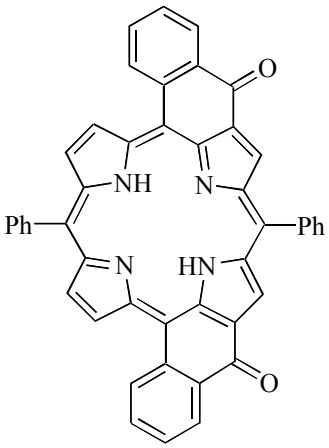
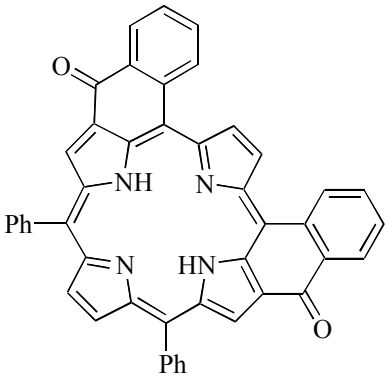
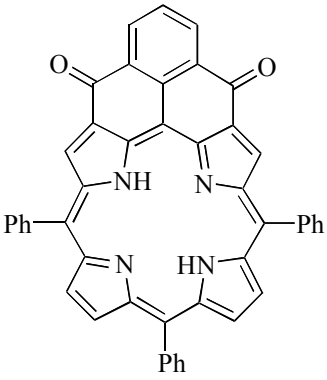


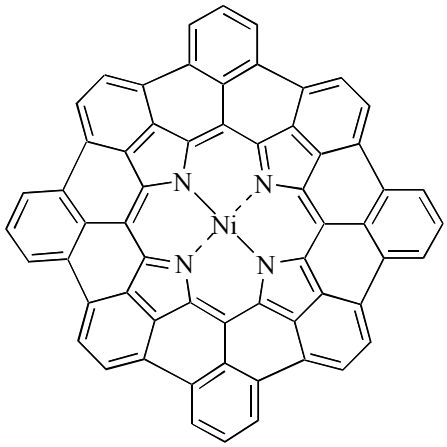
5.10



5.11

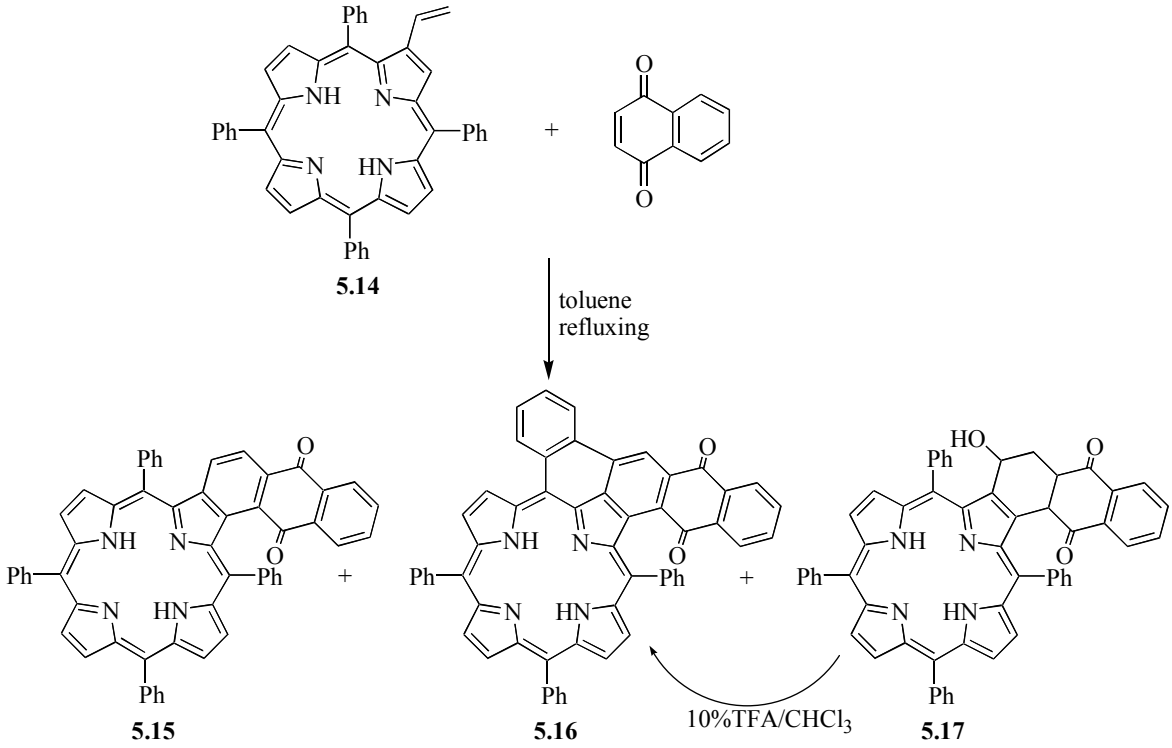


5.12



5.13

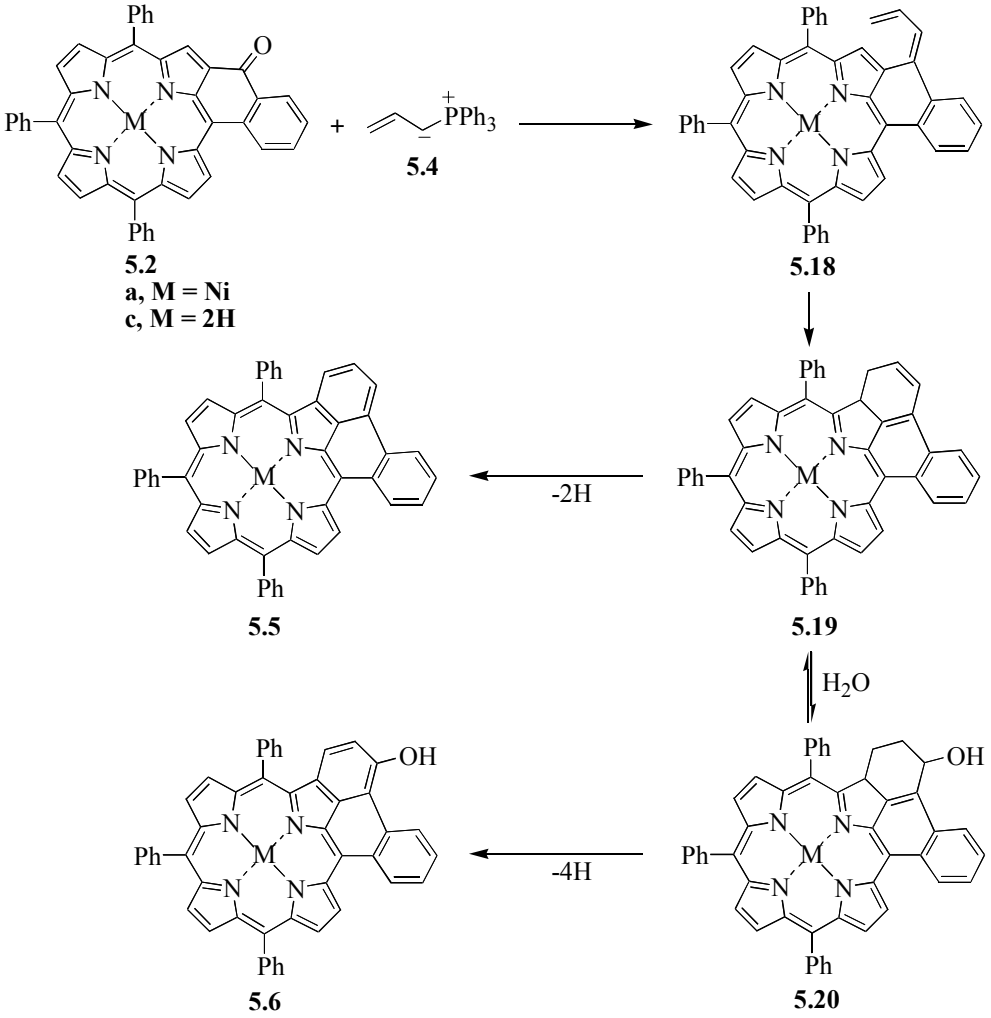
Similar results were observed when our group reinvestigated Diels-Alder reactions of β-vinyl-*meso*-tetraphenylporphyrin **5.14** with quinone derivatives.[21] The reaction of porphyrin **5.14** with 1,4-naphthoquinone was carried out in refluxing toluene (Scheme 5.6). The *meso*+β fused porphyrin **5.16** and porphyrin **5.17** were isolated from the reaction mixture, together with the expected porphyrin **5.15**. When treated with 10% trifluoroacetic acid (TFA) in chloroform, compound **5.17** was converted into the porphyrin derivative **5.16**.



5.14 **5.15** **5.16** **5.17**

Scheme 5.6

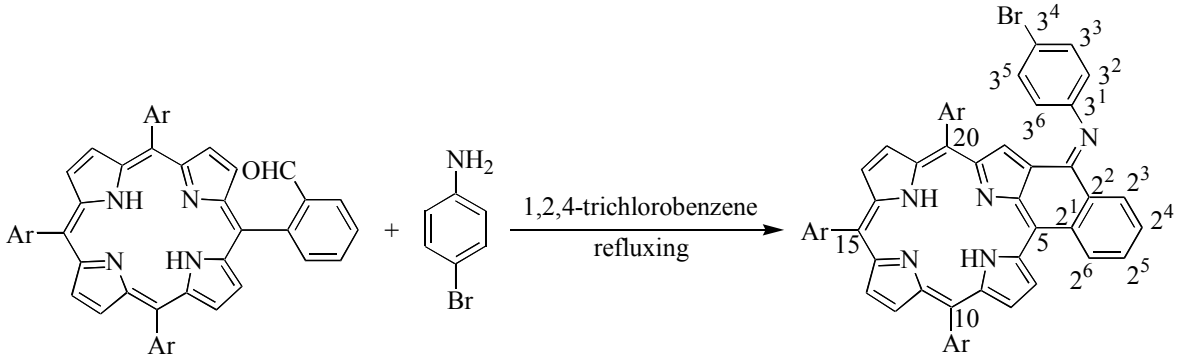
Therefore, a plausible mechanism for the reactions is proposed (Scheme 5.7). The Wittig reactions of porphyrins **5.2** with phosphorus ylide **5.4** afforded the porphyrins **5.18**. The ring-closed products **5.19** were obtained from the electrocyclic reaction of porphyrins **5.18**. The porphyrins **5.5** were the products of the aromatization of porphyrins **5.19**. However, the hydration of porphyrins **5.19** which has a styrene structure afforded porphyrins **5.20**. Porphyrins **5.6** were the aromatization products of porphyrins **5.20**, which are electron-rich and easy to oxidize. Since little or no water was available when sodium hydride was used as base, porphyrins **5.6** were obtained in low yields.



Scheme 5.7

5.3: Cyclization of imino porphyrin derivatives and their potential applications in the synthesis of polycyclic aromatic porphyrin analogues

We have synthesized β-imino porphyrin derivatives *in situ* from the condensation of β-formyl-*meso*-tetraphenylporphyrin with anilines and investigated their reactivities as heterodienes.[22] Interestingly, is it possible for imino porphyrin derivatives to form the cyclization products similar to porphyrins **5.2** obtained from β-formyl-*meso*-tetraphenylporphyrin? Since the cyclization products were not obtained from the condensation of β-formyl-*meso*-tetraphenylporphyrin with anilines in refluxing toluene, we then investigated the condensation of *meso*-(*o*-formylphenyl)porphyrins **2.14b** (Chapter 2) with 5 equivalents of *p*-bromoaniline in refluxing 1,2,4-trichlorobenzene for ten hours (Scheme 5.8). Indeed, a green cyclization product **5.21** was isolated in 47% yield and the starting porphyrin **2.14b** was recovered in 50%. The recovered starting porphyrin **2.14b** was confirmed by ^{1}H NMR study.

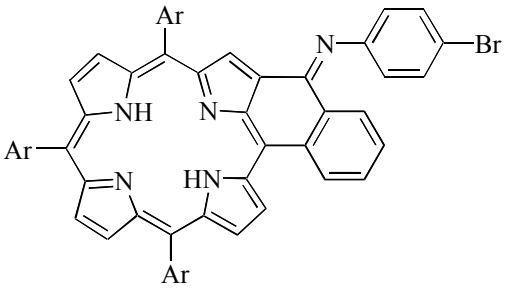


2.14b Ar = 2,3,6-$F_3C_6H_2$ **5.21**

Scheme 5.8

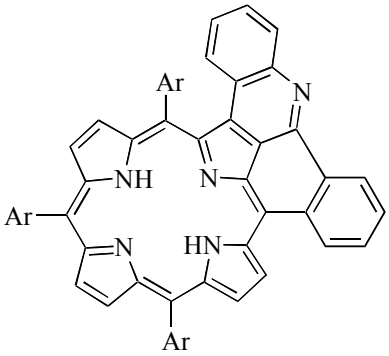
The structure of the new product was established by the UV-Vis, mass spectra and NMR (^{1}H, COSY, NOESY). Its UV-Vis spectrum also shows a pronounced red shift of both Soret and Q bands at λ_{max} 371, 458, 520, 560, 612 and 707 nm. The mass spectrum shows intense peaks at *m/z* 956 ($[M+H]^+$) and 955 ($[M]^{+\bullet}$), confirming that it is a cyclization product similar to **5.2**. In the ^{1}H NMR spectrum, the seven β-pyrrolic protons appear as one singlet at δ 7.76 ppm (H-2), one AB spin system at δ 8.62 ppm (2H, *J* 4.9 Hz), four doublets at δ 8.67 (*J* 4.9 Hz), 8.71 (*J* 4.9 Hz), 8.76 (*J* 5.0 Hz), 9.59 ppm (H-7, *J*

5.0 Hz). The two protons H-3^2 and H-3^6 appear as one doublet at δ 6.97 ppm (*J* 8.6 Hz), which is confirmed by a NOE cross peak between the H-3^2 (H-3^6) and the β-pyrrolic proton H-2. This fits only with structure **5.21**, and not with the isomeric porphyrin **5.22**. The two protons H-3^3 and H-3^5 appear as one doublet at δ 7.56 ppm (*J* 8.6 Hz). The proton H-2^6 appears as one doublet at δ 8.46 ppm (*J* 7.5 Hz), which is confirmed by a NOE cross peak between the proton H-2^6 and the β-pyrrolic proton H-7. The proton H-2^5 appears as one double triplet at δ 7.83 ppm (*J* 1.4 and 7.5 Hz). The proton H-2^3 appears as one double doublet at δ 8.89 ppm (*J* 1.4 and 7.9 Hz). The proton H-2^4 and three protons of the *meso*-aryl groups appear as one multiplet at δ 7.58-7.73 ppm. The other three protons of the *meso*-aryl groups appear as one multiplet at δ 7.29-7.35 ppm.

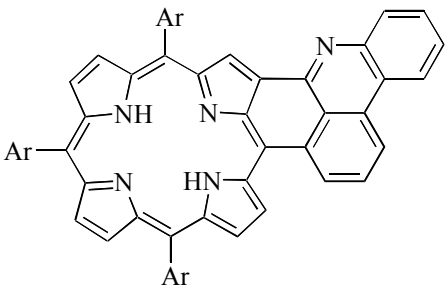


5.22 Ar = 2,3,6-$F_3C_6H_2$

Palladium-assisted intramolecular aryl-aryl coupling reactions have been used to synthesize polycyclic aromatic hydrocarbons (PAHs).[23] The analogues of structures of porphyrins **5.21** and **5.22** have potential use as starting porphyrins to synthesize the polycyclic aromatic porphyrin analogues **5.23** and **5.24**, which will be investigated in the near future.



5.23



5.24

5.4: Conclusion

The novel polycyclic aromatic porphyrin analogues **5.5** and **5.6** have been synthesized from the reactions of ketone-bridged porphyrins **5.2** with phosphorus ylide **5.4**. The porphyrin analogues **5.5** and **5.6** have potential applications in PDT treatment and NIR absorption materials due to the red shift of their Soret and Q bands.

The green cyclization product **5.21** was obtained from the reaction of porphyrin **2.14b** with *p*-bromoaniline in refluxing 1,2,4-trichlorobenzene. Porphyrin **5.21** and its isomer **5.22** have potential use as starting materials to synthesize polycyclic aromatic porphyrin analogues **5.23** and **5.24**.

5.5: Experimental Section

5.5.1: General

^{1}H and ^{13}C NMR spectra were recorded on Bruker Avance 300 spectrometer and Bruker Avance 500 spectrometer at 300.13 (500.13) and 75.47 (125.77) MHz, respectively. $CDCl_3$ was used as solvent and TMS as internal reference; the chemical shifts are expressed in δ (ppm) and the coupling constants (*J*) in Hertz [Hz]. Unequivocal ^{1}H assignments were made with aid of 2D COSY ($^{1}H/^{1}H$) and NOESY spectra (mixing time of 800 ms), while ^{13}C assignments were made on the basis of 2D HSQC and HMBC (delays for long-range *J* C/H couplings were optimized for 7 Hz) experiments. Mass spectra were recorded on VG AutoSpec Q mass spectrometer using $CHCl_3$ as solvent and 3-nitrobenzyl alcohol (NBA) as matrix. The UV-Vis spectra were recorded on a Uvikon spectrophotometer using $CHCl_3$ as solvent. Column chromatography was carried out using silica gel (Merck, 35-70 mesh). Preparative thin-layer chromatography was carried out on 20 × 20 cm glass plates coated with Merck 60 silica gel (2 mm thick). Analytical TLC was carried out on precoated sheets with silica gel (Merck 60, 0.2 mm thick).

5.5.2: Nickel(II) 2-formyl-*meso*-tetraphenylporphyrin 5.1a

To a suspension of nickel(II) tetraphenylporphyrin (NiTPP, 0.32 g, 0.48 mmol) in 1,2-dichloroethane (50 mL) was added dry *N*,*N*-dimethylformamide (DMF, 2.6 mL) and phosphorus oxychloride (2.0 mL). The mixture was brought to reflux overnight. The solution poured into saturated sodium bicarbonate solution (100 mL) and warmed to complete neutralization. After 2 hours, the organic phase was decanted, washed with water (3 × 100 mL), dried (Na_2SO_4). The porphyrin **5.1a** (0.26 g, 78% yield) was isolated by chromatography using a mixture of chloroform/light petroleum (2:1) as eluent.

UV-Vis ($CHCl_3$) λ_{max} (% rel. intensity) 430 (100%), 541 (11%), 583 (9%) nm.
^{1}H NMR ($CDCl_3$) δ: 7.66-7.75 (m, 12H, Ph-H$_{meta,para}$), 7.94-8.04 (m, 8H, Ph-H$_{ortho}$), 8.66-8.77 (m, 6H, β-H), 9.16 (s, 1H, β-H), 9.31 (s, 1H, C*H*O).

5.5.3: Copper(II) 2-formyl-*meso*-tetraphenylporphyrin 5.1b

To a suspension of copper(II) tetraphenylporphyrin (CuTPP, 0.32 g, 0.47 mmol) in 1,2-dichloroethane (50 mL) was added dry *N*,*N*-dimethylformamide (DMF, 2.6 mL) and phosphorus oxychloride (2.0 mL). The mixture was brought to reflux overnight. The solution poured into saturated sodium bicarbonate solution (100 mL) and warmed to complete neutralization. After 2 hours, the organic phase was decanted, washed with water (3 × 100 mL), dried (Na_2SO_4). The porphyrin **5.1b** (0.31 g, 93% yield) was isolated by chromatography using a mixture of chloroform/light petroleum (2:1) as eluent.

UV-Vis ($CHCl_3$) λ_{max} (% rel. intensity) 427 (100%), 551 (7%), 592 (6%) nm.
MS (FAB^+) 704 $(M+H)^+$, 703 $M^{+\bullet}$.

5.5.4: Synthesis of ketone 5.2a

Nickel(II) 2-formylTPP **5.1a** (0.15 g) was added to a solution of 4-toluenesulfonic acid monohydrate (0.03 g) and *p*-chloranil (0.11 g) in 1,2-dichloroethane (10 mL). After 2 hours at reflux, the organic phase was washed with saturated sodium bicarbonate solution (10 mL) and water (3 × 10 mL) and then it was dried (Na_2SO_4). The porphyrin **5.2a** (0.06 g, 40% yield) was isolated by chromatography using a mixture of chloroform/light petroleum (2:1) as eluent.

UV-Vis ($CHCl_3$) λ_{max} (% rel. intensity) 380 (32%), 463 (100%), 646 (16%) nm.

^{1}H NMR ($CDCl_3$) δ: 7.37 (dt, 1H, fused Ph-H, *J* 0.9 and 7.5 Hz), 7.56-7.70 (m, 10H, fused Ph-H and Ph-$H_{meta,para}$), 7.78-7.88 (m, 7H, fused Ph-H and Ph-H_{ortho}), 8.31-8.36 (m, 3H, fused Ph-H and β-H), 8.43 (d, 1H, β-H, *J* 5.0 Hz), 8.45 (d, 1H, β-H, *J* 5.0 Hz), 8.53 (d, 1H, β-H, *J* 5.1 Hz), 9.06 (s, 1H, β-H), 9.08 (d, 1H, β-H, *J* 5.1 Hz).
MS (FAB^+) 697 $(M+H)^+$, 696 $M^{+\bullet}$.

5.5.5: Synthesis of ketone 5.2b

Copper(II) 2-formylTPP **5.1b** (0.15 g) was added to a solution of 4-toluenesulfonic acid monohydrate (0.03 g) and *p*-chloranil (0.11 g) in 1,2-dichloroethane (10 mL). After 2 hours at reflux, the organic phase was washed with saturated sodium bicarbonate solution (10 mL) and water (3 × 10 mL) and then it was dried (Na_2SO_4). The porphyrin **5.2b** (0.07 g, 47% yield) was isolated by chromatography using a mixture of chloroform/light petroleum (2:1) as eluent.

UV-Vis ($CHCl_3$) λ_{max} (% rel. intensity) 388 (30%), 461 (100%), 595 (7%), 649 (14%), 687 (11%) nm.
MS (FAB^+) 702 $(M+H)^+$, 701 $M^{+\bullet}$.

5.5.6: Demetalation of ketone 5.2b

Ketone **5.2b** (100 mg) was dissolved in dichloromethane (20 mL) and sulfuric acid (2 mL) was added at room temperature. After 10 minutes, the resulting solution was poured into cooled aqueous sodium bicarbonate solution, extracted with dichloromethane (3 × 10 mL), washed with water (3 × 10 mL), dried (Na_2SO_4). The porphyrin **5.2c** (87 mg, 95% yield) was isolated by chromatography using a mixture of chloroform/light petroleum (2:1) as eluent.

UV-Vis ($CHCl_3$) λ_{max} (% rel. intensity) 379 (32%), 462 (100%), 577 (6%), 638 (8%), 740 (9%) nm.

^{1}H NMR ($CDCl_3$) δ: -0.68 (s, 2H, N*H*), 7.35 (t, 1H, fused Ph-H, *J* 7.6 Hz), 7.59 (dt, 1H, fused Ph-H, *J* 1.0 and 7.6 Hz), 7.66-7.78 (m, 9H, Ph-$H_{meta,para}$), 8.04-8.10 (m, 6H, Ph-H_{ortho}), 8.14 (d, 1H, fused Ph-H, *J* 7.6 Hz), 8.37 (dd, 1H, fused Ph-H, *J* 1.0 and 7.6 Hz), 8.47 (d, 1H, β-H, *J* 4.8 Hz), 8.51-8.58 (m, 4H, β-H), 9.14 (d, 1H, β-H, *J* 5.0 Hz), 9.18 (s, 1H, β-H).

MS (FAB^+) 641 $(M+H)^+$, 640 $M^{+\bullet}$.

5.5.7: Allyltriphenylphosphonium bromide 5.3

A mixture of allyl bromide (0.43 mL, 5 mmol) and triphenylphosphine (1.31 g, 5 mmol) in ethyl acetate (20 mL) was stirred at room temperature for three days. Light petroleum (60 mL) was added and the precipitated solid was collected and washed with light petroleum (20 mL) to give phosphonium salt **5.3** (1.70 g, 89% yield) as a white solid.

mp 223-225 ^oC (lit.[24] mp 225-227 ^oC).

^{1}H NMR ($CDCl_3$) δ: 4.83 (dd, 2H, C*H*$_2$, *J* 6.7 and 15.6 Hz), 5.38-5.43 (m, 1H, alkenyl-H), 5.56-5.77 (m, 2H, alkenyl-H), 7.69-7.89 (m, 15H, Ph-H).

5.5.8: Reaction of ketone 5.2a with allylic phosphorus ylide 5.4 using NaH as base

A toluene (5 mL) solution of ketone **5.2a** (20 mg), phosphonium salt **5.3** (22 mg, 2 equiv.) and sodium hydride (60%, 5 mg, 4 equiv.) was heated at reflux for 12 hours. The solution was diluted with $CHCl_3$ (30 mL) and washed with 1 N hydrochloric acid (10 mL) and water (3 × 10 mL), then it was dried (Na_2SO_4). The solvent was evaporated under vacuum, and the residue was subjected to column chromatography (silica gel) using a mixture of chloroform-light petroleum (2:1) as eluent. The first fraction to be collected was

porphyrin **5.5a** (3.3 mg, 16% yield), then the second fraction isolated was a complicated mixture in trace amounts, porphyrin **5.6a** (0.7 mg, 3% yield) was obtained as the third fraction.

5.5a:

UV-Vis ($CHCl_3$) λ_{max} (% rel. intensity) 445 (100%), 562 (7%), 612 (10%) nm.

^{1}H NMR ($CDCl_3$) δ: 7.35 (d, 1H, H-2^1, *J* 7.7 Hz), 7.66-7.70 (m, 6H, Ph-H$_{meta,para}$), 7.78-7.85 (m, 4H, H-2^5 or H-2^6, and Ph-H$_{meta,para}$), 7.93-7.98 (m, 1H, H-2^6 or H-2^5), 7.98-8.03 (m, 7H, H-2^2 and Ph-H$_{ortho}$), 8.53 (d, 1H, β-H, *J* 4.8 Hz), 8.60 (d, 1H, β-H, *J* 4.8 Hz), 8.67 (AB, 2H, *J* 4.9 Hz), 8.88 (d, 1H, H-2^3, *J* 7.7 Hz), 8.89 (d, 1H, β-H, *J* 4.9 Hz), 8.98 (d, 2H, H-2^4 and H-2^7, *J* 8.1 Hz), 9.51 (d, 1H, *J* 4.9 Hz).

MS (FAB$^+$) 719 $(M+H)^+$, 718 $M^{+\bullet}$.

5.6a:

UV-Vis ($CHCl_3$) λ_{max} (% rel. intensity) 444 (100%), 558 (5%), 617 (8%) nm.

^{1}H NMR ($CDCl_3$) δ: 6.23 (br s, 1H, O*H*), 7.04 (d, 1H, H-2^1, *J* 8.2 Hz), 7.11 (d, 1H, H-2^2, *J* 8.2 Hz), 7.61-7.89 (m, 11H, H-2^5, H-2^6, and Ph-H$_{meta,para}$), 7.91-7.99 (m, 6H, Ph-H$_{ortho}$), 8.52 (d, 1H, β-H, *J* 4.8 Hz), 8.58 (d, 1H, β-H, *J* 4.8 Hz), 8.59 (d, 1H, β-H, *J* 4.8 Hz), 8.64 (d, 1H, β-H, *J* 4.8 Hz), 8.83 (d, 1H, β-H, *J* 4.9 Hz), 8.86 (d, 1H, H-2^7, *J* 7.8 Hz), 9.39 (d, 1H, β-H, *J* 4.9 Hz), 9.55 (d, 1H, H-2^4, *J* 7.8 Hz).

MS (FAB$^+$) 735 $(M+H)^+$, 734 $M^{+\bullet}$.

5.5.9: Reaction of ketone 5.2a with allylic phosphorus ylide 5.4 using K_2CO_3 as base

A toluene (5 mL) solution of ketone **5.2a** (20 mg), phosphonium salt **5.3** (22 mg, 2 equiv.) and potassium carbonate (8 mg, 2 equiv.) was heated at reflux for two days. After the solution was cooled to room temperature, the solvent was evaporated under vacuum, and the residue was subjected to column chromatography (silica gel) using a mixture of chloroform-light petroleum (2:1) as eluent. The first fraction to be collected was porphyrin

5.5a (2.2 mg, 12% yield), then, the second fraction isolated was porphyrin **5.6a** (5.7 mg, 27% yield).

5.5.10: Reaction of ketone 5.2c with allylic phosphorus ylide 5.4 using NaH as base

A toluene (5 mL) solution of ketone **5.2c** (20 mg), phosphonium salt **5.3** (24 mg, 2 equiv.) and sodium hydride (60%, 5 mg, 4 equiv.) was heated at reflux for 12 hours. The solution was diluted with $CHCl_3$ (30 mL) and washed with 1 N hydrochloric acid (10 mL) and water (3 × 10 mL), then it was dried (Na_2SO_4). The solvent was evaporated under vacuum, and the residue was subjected to column chromatography (silica gel) using a mixture of chloroform-light petroleum (2:1) as eluent. The first fraction to be collected was porphyrin **5.5c** (2.5 mg, 12%), then the second fraction isolated was a complicated mixture in trace amounts, and porphyrin **5.6c** (0.7 mg, 3%) was obtained as the third fraction.

5.5c:

UV-Vis ($CHCl_3$) λ_{max} (% rel. intensity) 445 (100%), 546 (5%), 588 (7%), 615 (5%), 671 (4%) nm.

^{1}H NMR (500 MHz, $CDCl_3$-TFA) δ: 7.94-8.05 (m, 10H, H-2^1 and Ph-H), 8.11 (dt, 1H, H-2^5, *J* 0.9 and 7.5 Hz), 8.21 (dd, 1H, β-H, *J* 1.6 and 4.6 Hz), 8.25 (dd, 1H, β-H, *J* 1.7 and 4.5 Hz), 8.27 (d, 1H, β-H, *J* 4.8 Hz), 8.29-8.34 (m, 3H, H-2^6 and Ph-H), 8.39 (dd, 1H, β-H, *J* 1.4 and 4.6 Hz), 8.39-8.42 (m, 2H, Ph-H), 8.44 (t, 1H, H-2^2, *J* 7.7 Hz), 8.52 (d, 1H, β-H, *J* 4.8 Hz), 8.55-8.57 (m, 2H, Ph-H), 8.93 (dd, 1H, β-H, *J* 1.4 and 4.5 Hz), 9.30 (d, 1H, H-2^4, *J* 7.8 Hz), 9.41 (d, 1H, H-2^3, *J* 7.7 Hz), 9.81 (d, 1H, H-2^7, *J* 8.1 Hz).

^{13}C NMR (126 MHz, $CDCl_3$-TFA) δ: 107.1, 114.6, 120.0, 124.8, 125.5, 125.6, 125.7, 126.2, 126.9, 127.6, 127.7, 128.1, 128.5, 128.8, 128.9, 129.0, 129.4, 129.6, 130.3, 130.6, 131.3, 131.5, 131.8, 132.0, 132.9, 133.7, 134.6, 137.3, 137.5, 138.7, 138.98, 139.05, 141.2, 141.8, 143.2, 146.0, 146.06, 146.11, 151.1.

MS (FAB^+) 663 $(M+H)^+$, 662 $M^{+\bullet}$.

5.6c:

UV-Vis ($CHCl_3$) λ_{max} (% rel. intensity) 444 (100%), 548 (5%), 588 (8%), 613 (6%), 668 (5%) nm.

^{1}H NMR ($CDCl_3$-TFA) δ: 6.74 (d, 1H, H-2^1, *J* 8.4 Hz), 7.35 (d, 1H, H-2^2, *J* 8.4 Hz), 7.63 (t, 1H, Ph-H, *J* 7.6 Hz), 7.92-8.01 (m, 6H, Ph-H), 8.03-8.09 (m, 3H, Ph-H), 8.16-8.30 (m, 6H, Ph-H and β-H), 8.38-8.41 (m, 2H, Ph-H), 8.47 (d, 1H, β-H, *J* 4.4 Hz), 8.55 (d, 1H, β-H, *J* 5.0 Hz), 8.57-8.60 (m, 2H, Ph-H), 8.77 (d, 1H, β-H, *J* 4.2 Hz), 8.89 (d, 1H, H-2^4, *J* 8.1 Hz), 9.72 (d, 1H, H-2^7, *J* 8.3 Hz).

MS (FAB$^+$) 679 $(M+H)^+$, 678 $M^{+\bullet}$.

5.5.11: Reaction of ketone 5.2c with allylic phosphorus ylide 5.4 using K_2CO_3 as base

A toluene (5 mL) solution of ketone **5.2c** (20 mg), phosphonium salt **5.3** (24 mg, 2 equiv.) and potassium carbonate (9 mg, 2 equiv.) was heated at reflux for two days. After the solution was cooled to room temperature, the solvent was evaporated under vacuum, and the residue was subjected to column chromatography (silica gel) using a mixture of chloroform-light petroleum (2:1) as eluent. The first fraction to be collected was porphyrin **5.5c** (5.3 mg, 26% yield), the second fraction isolated was a complicated mixture in trace amounts, porphyrin **5.6c** (4.0 mg, 19% yield) was obtained as the third fraction.

5.5.12: Cyclization of imino porphyrin derivative

A 1,2,4-trichlorobenzene (5 mL) solution of porphyrin **2.14b** (10 mg), *p*-bromoaniline (11 mg, 5 equiv.) was heated at reflux for ten hours. After the solution was cooled to room temperature, the solution was subjected to column chromatography (silica gel) using chloroform as eluent. The first fraction to be collected was a green compound **5.21** (5.6 mg, 47% yield), the second fraction isolated was recovered starting porphyrin **2.14b** (5.0 mg, 50%).

UV-Vis ($CHCl_3$) λ_{max} (% rel. intensity) 371 (21%), 458 (100%), 520 (5%), 560 (7%), 612 (7%), 707 (5%) nm.

^{1}H NMR ($CDCl_3$) δ: 1.27 (s, 2H, N*H*), 6.97 (d, 2H, H-3^2 and H-3^6, *J* 8.6 Hz), 7.29-7.35 (m, 3H, Ph-H), 7.56 (d, 2H, H-3^3 and H-3^5, *J* 8.6 Hz), 7.58-7.73 (m, 4H, H-2^4 and Ph-H), 7.76 (s, 1H, β-H), 7.83 (dt, 1H, H-2^5, *J* 1.4 and 7.5 Hz), 8.46 (d, 1H, H-2^6, *J* 7.5 Hz), 8.62 (AB, 2H, β-H, *J* 4.9 Hz), 8.67 (d, 1H, β-H, *J* 4.9 Hz), 8.71 (d, 1H, β-H, *J* 4.9 Hz), 8.76 (d, 1H, β-H, *J* 5.0 Hz), 8.89 (dd, 1H, H-2^3, *J* 1.4 and 7.9 Hz), 9.59 (d, 1H, β-H, *J* 5.0 Hz).

MS (FAB$^+$) 956 $(M+H)^+$, 955 $M^{+\bullet}$.

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